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Research article

Comparison of intranasal dexmedetomidine alone and dexmedetomidine-chloral hydrate combination sedation for electroencephalography in children: A large retrospective cohort study and propensity score-matched analysis

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ABSTRACT

Aim: To compare the safety and efficacy of intranasal high-dose dexmedetomidine (DEX) versus a combination of intranasal low-dose dexmedetomidine and oral chloral hydrate (DEX-CH) sedation during electroencephalography (EEG) in children.

Methods: Unadjusted analysis, 1:1 propensity score matching (PSM), and inverse probability of treatment weighting (IPTW) were used to compare the sedation success rate, adverse effects, onset time, and recovery time of these two sedation methods for 6967 children who underwent EEG.

Results: A total of 6967 children were enrolled in this study, of whom 846 (12.1 %) underwent DEX intranasal sedation while 6121 (87.9 %) received DEX-CH sedation. No significant differences were observed in the sedation success rate with the first dose between the two groups [824 (97.4 %) for DEX vs. 5971 (97.6 %) for DEX-CH; RR 0.99; 95 % CI, 0.98–1.01; P = 0.79]. Similarly, there were no notable disparities in the incidence of adverse events [16 (1.9 %) for DEX vs. 101 (1.7 %) for DEX-CH; RR 1.15; 95 % CI, 0.68–1.93; P = 0.32]. However, intranasal DEX sedation compared with DEX-CH sedation was associated with lower vomiting [0 vs. 95(1.6 %); RR 0.04; 95 % CI, 0.02–0.6; P = 0.02] or more bradycardia [13(1.5 %) vs. 2(0.03 %); RR 47.03; 95 % CI, 10.63–208.04; P < 0.001]. Multivariate analysis using PSM and IPTW analysis yielded similar results.

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Conclusion: Both methods for EEG had high sedation success rate and low incidence of adverse events. High-dose intranasal DEX was more likely to induce bradycardia and had a shorter recovery time than the DEX-CH sedation, which was more likely to induce vomiting.

1. Introduction

Electroencephalography (EEG) is an essential tool for diagnosing neurological diseases. Sedation is necessary for children who are uncooperative with the EEG setup and those who need sleep EEG. Satisfactory sedation can make the examination process more efficient and smoother.

Sedative drugs used for EEG are required to have no or minimal effect on the background and epileptic discharges of the EEG [1]. Many sedative drugs that act on the central nervous system interfere with brain waves, such as ketamine, propofol, and sevoflurane [2,3]. Previous studies had shown that both chloral hydrate (CH) and dexmedetomidine (DEX) were utilized for sedation during EEG, and didn't interfere with brainwaves [4].

CH is a commonly administered sedative in EEG, which has been used for over 60 years and remains useful in the present day [5]. The recommended dose for use alone is 40–100 mg/kg [6]. But for some children, even if the maximum doses were used, sedation still fails. At the same time, high doses (70–100 mg/kg) are more likely to cause adverse events such as long action duration, inhibition of circulation and respiration, oxygen desaturation and airway obstruction. It is also worth noting that CH might pose a potential cancer risk to humans [7,8]. So, some literatures recommend low-dose CH combination with other sedative drugs to reduce the risk of adverse events [9,10].

DEX, a highly selective central alpha-2 agonist, has been proven to be a suitable sedative agent, which produces a state similar to natural sleep and interferes little with the basic background waves [11]. However, the use of high doses may also lead to adverse events such as hypotension and bradycardia. In our center, DEX is the next commonly used drug for EEGs.

Razieh Fallah et al. reported CH in a dosage of 40 mg/kg is safer and combination with DEX might decrease its dosage [12]. Since 2018, EEGs have been widely conducted in our center using oral low doses (30 mg/kg) CH combination with intranasal (2 μg/kg) DEX. Until today, most anesthesiologists have still used this combination as the EEG sedative. The main reason is that they think the combination of two low-dose drugs can reduce adverse events occurring in high doses used alone. But on the other hand, some anesthesiologists insist on using intranasal DEX alone.

Based on a large sample size each year in our center, the largest number of sedations in China, this research aimed to compare the effectiveness and safety of intranasal high-doses (3 μg/kg) DEX alone and intranasal DEX combination with oral CH (DEX-CH) in children EEG sedation.

2. Methods

Ethical approval for this propensity score matched, retrospective cohort study ((2024) Year Aaron trial (research) No.3) was provided by the Ethics Committee of the Children's Hospital affiliated with Chongqing Medical University, Chongqing, China (Chairperson Hongmei Xu) on March 4, 2024.

In this retrospective study, we collected the maintained database of consecutive patients sedated for EEG between January 2018 and December 2022 in our center. The inclusion criteria included children who underwent EEG and received intranasal DEX sedation or DEX-CH sedation. Exclusion criteria were difficult airway, severe liver or renal insufficiency, severe bradycardia, and incomplete data. Data used in the current study were from our specialized sedation electronic system.

All sedation procedures were performed according to protocols. The anesthesiologists evaluated and ordered. All drugs were administered by the nurse anesthetist after the patients fast for 1 h, the minimum fasting time. For children who received intranasal DEX sedation, a nurse anesthetist administered 3 μg/kg of intranasal DEX. For DEX-CH sedation, 30 mg/kg of oral CH and then 2 μg/kg of intranasal DEX were administered to children. Sedation depth was assessed using Modified Observer Assessment of Alertness/Sedation Scale (MOAA/S) [13]. We defined the successful sedation as the MOAA/S score less than or equal to 3 within 30 min and completed EEG without rescue drugs. If the MOAA/S score was greater than 3 within 30 min after sedation, a rescue drug would be given, including additional intranasal DEX and oral CH. If the EEG could still not be completed, inhaled sevoflurane was administered, and this was defined as failed sedation. We defined the onset time of sedation as the time from drug administration to MOAA/S score less than or equal to 3. Recovery time was defined as the time from MOAA/S score less than or equal to 3 to recovery.

The primary outcome measure was the success rate of sedation. Secondary outcome measures included onset time of sedation, recovery time, and adverse event.

The classification and severity of adverse events are according to the TROOPS Comprehensive Research Tool (www.TROOPS-sedation.com) [14]. The adverse events were defined as the following manners: (1) Oxygen desaturation, oxygen saturation is less than 90 % for more than 30 s; (2) recovery delay, defined as a sedation recovery time >2 h; (3) bradycardia, defined as a heart rate deceleration of greater than 20 % of the baseline; (4) upper airway obstructions (without airway interventions, and recovered by airway repositioning, supplemental oxygen, and suctioning).

3. Data analysis

Baseline characteristics were summarized as the number (percentage) and were compared between intervention groups using χ^2 tests. In the unmatched sample, there may be significant differences in baseline characteristics between the two groups. After one-to-one propensity score matching and inverse probability of treatment weighting, these imbalances differences were eliminated on baseline characteristics. Given that sedation protocol was not randomly allocated to participants, two propensity score-based approaches were applied to reduce the effects of confounding in comparing non-randomized treatments: propensity score matching (PSM) and inverse probability treatment weighting (IPTW). The individual propensity score for the current study represented the probability of receiving DEX sedation, estimated using a multivariable logistic regression model adjusting for observed variables. In the PSM analysis, the patients who received DEX sedation and those who received DEX-CH sedation were matched 1:1 ratio without replacement using a nearest neighbor algorithm within a caliper width equal to 0.2 of the standard deviation of the logit of the calculated propensity score. In the IPTW analysis, stabilized weights were utilized. Specifically, for the DEX sedation group, weights were determined by multiplying the proportion of patients receiving DEX sedation with the inverse of each patient's propensity score. For the DEX-CH sedation group, weights were calculated by multiplying the proportion of patients undergoing DEX-CH sedation with the inverse of (1 minus the propensity score). To check the quality of matching, we compared the standardized mean difference (SMD) of each covariate between the intranasal DEX group and the DEX-CH sedation group. SMDs exceeding 0.1 were widely regarded as indicators of substantial imbalances. The correlation between sedation methods, unsuccessful sedation, and sedation-related complications was evaluated by calculating relative risks (RR) and confidence intervals (CI) through log binomial regression analysis. To compare the induction time, and the recovery time between the intranasal DEX group and the DEX-CH sedation group, linear regression models also were performed. Two-sided P values of less than 0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (Copyright ©2016 SAS Institute Inc. Cary, NC, USA).

4. Result

In our cohort, 6967 children were enrolled, 846 (12.1 %) received intranasal DEX sedation and 6121 (87.9 %) received DEX-CH sedation. The flow chart of the study had been presented in Fig. 1. The distribution of the participants' baseline characteristics according to sedation protocols was summarized in Table 1.

On unadjusted analysis, there was no significant association between sedation protocols and successful sedation rate with first doses [824(97.4 %) vs. 5971(97.6 %); RR 0.99; 95 % CI, 0.98–1.01; P = 0.79] or incidence of adverse events [16(1.9 %) vs. 101(1.7 %); RR 1.15; 95 % CI, 0.68–1.93; P = 0.32]. Intranasal DEX sedation compared with DEX-CH sedation was associated with lower vomiting [0 vs. 95(1.6 %); RR 0.04; 95 % CI, 0.02–0.6; P = 0.02] or more bradycardia [13(1.5 %) vs. 2(0.03 %); RR 47.03; 95 % CI, 10.63–208.04; P < 0.001], which had been shown in Table 2. There was no significant difference in sedation onset time between the two groups, but the recovery time was slightly longer in the DEX-CH group, which had been shown in Table 3. Multivariable analysis

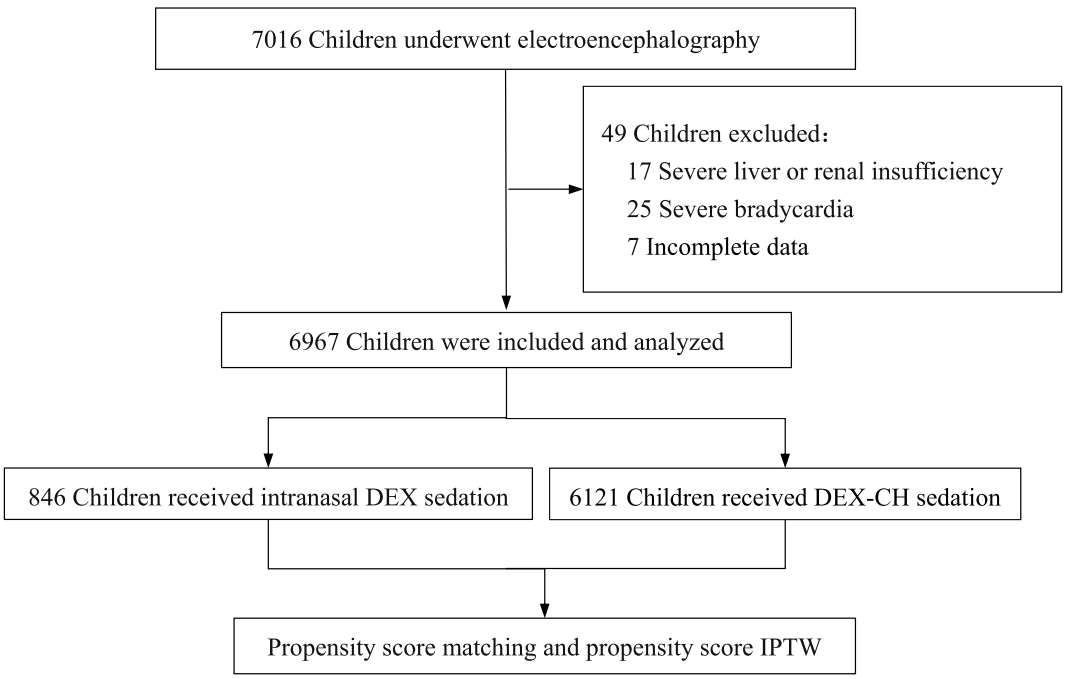

Fig. 1. Flow diagram of the study. DEX, dexmedetomidine; DEX-CH, dexmedetomidine and oral chloral hydrate combination; IPTW, inverse probability of treatment weighting.

Table 1
Baseline subject characteristics (n = 6967). Baseline characteristics in table were presented as the number (percentage), and were compared between intervention groups using χ^2 tests.

Characteristic	Unweighted Sample			Propensity 1:1 Matching			IPTW		
	DEX (n = 846)	DEX-CH (n = 6121)	SMD	DEX (n = 806)	DEX-CH (n = 806)	SMD	DEX (n = 6744)	DEX-CH (n = 6988)	SMD
Age[a]									
≤1 year	31(3.7)	196(3.2)	0.025	31(3.9)	33(4.1)	0.012	309.1(4.6)	240.9(3.5)	0.058
1–3 years	138(16.3)	1109(18.1)	0.048	138(17.1)	156(19.4)	0.058	1362.7 (20.2)	1258.4(18.0)	0.056
3–6 years	351(41.5)	2501(40.9)	0.021	335(41.6)	318(39.5)	0.043	2585.9 (38.3)	2850.5(40.8)	0.050
6–12 years	283(33.5)	2088(34.1)	0.014	259(32.1)	269(33.3)	0.026	2254.1 (33.4)	2370.4(33.9)	0.011
12–18 years	43(5.1)	227(3.7)	0.067	43(5.3)	30(3.7)	0.077	233.0(3.5)	268.1(3.8)	0.020
Male	556(65.7)	4143(67.7)	0.042	527(65.4)	533(66.1)	0.005	4455.2 (66.1)	4708.2(67.4)	0.028
Weight									
≤10 kg	56(6.6)	454(7.4)	0.031	56(6.9)	67(8.3)	0.051	662.1(9.8)	531.7(7.6)	0.078
10.1–20 kg	452(53.4)	3368(55.0)	0.032	437(54.2)	442(54.8)	0.012	3609.8 (53.5)	3822.0(54.7)	0.023
20.1–30 kg	239(28.3)	1583(25.9)	0.054	215(26.7)	197(24.4)	0.051	1581.9 (23.5)	1812.3(25.9)	0.058
>30 kg	99(11.7)	716(11.7)	0	98(12.2)	100(12.4)	0.008	891.0(13.2)	822.1(11.8)	0.044
Diagnosis									
Epilepsy	272(32.2)	1638(26.8)	0.118	239(29.7)	240(29.8)	0.003	1889.3 (28.0)	1914.1(27.4)	0.014
Febrile convulsion	69(8.2)	516(8.4)	0.009	69(8.6)	64(7.9)	0.023	572.6(8.5)	584.2(8.4)	0.005
Developmental behavioral disease	347(41.0)	3156(51.6)	0.213	342(42.4)	331(41.1)	0.028	3135.4 (46.5)	3495.9(50.0)	0.071
Others	158(18.7)	811(13.3)	0.149	156(19.4)	171(21.2)	0.047	1147.7 (17.0)	993.9(14.2)	0.077
ASA									
I	516(61.0)	532(8.7)	0.667	476(59.1)	473(58.7)	0.008	1062.7 (15.8)	1070.6(15.3)	0.012
II	326(38.5)	5546(90.6)	1.298	326(40.5)	330(40.9)	0.010	5638.0 (83.6)	5870.6(84.0)	0.011
III	4(0.5)	43(0.7)	0.030	4(0.5)	3(0.4)	0.020	44.2(0.6)	47.0(0.7)	0.002
Fasting time									
≤2 h	223(26.4)	1702(27.8)	0.033	212(26.3)	217(26.9)	0.014	1894.3 (28.1)	1927.88(27.6)	0.011
2–4 h	387(45.7)	2892(47.3)	0.030	375(46.5)	363(45.0)	0.029	3055.3 (45.3)	3287.05(47.0)	0.035
4–6 h	49(5.8)	334(5.5)	0.014	46(5.7)	58(7.2)	0.061	495.2(7.3)	393.2(5.6)	0.069
>6 h	187(22.1)	1193(19.5)	0.064	173(21.5)	168(20.8)	0.015	1300.1 (19.3)	1380.11(19.8)	0.012
Allergy	8(0.9)	78(1.3)	0.031	8(1.0)	6(0.7)	0.025	73.01(1.1)	114.53(1.6)	0.048
Respiratory illness	21(2.5)	156(2.6)	0.004	21(2.6)	26(3.2)	0.008	194.97(2.9)	182.05(2.6)	0.017
Underlying health risk[b]	46(5.4)	212(3.5)	0.096	46(5.7)	39(4.8)	0.027	321.1(4.8)	278.4(4.0)	0.038
Previous sedation	204(24.1)	1798(29.4)	0.119	204(25.31)	235(29.2)	0.086	1902.62 (28.2)	2086.1(29.9)	0.036
Sleep deprivation	164(19.4)	1174(19.2)	0.005	161(20.0)	163(20.2)	0.003	1453.9 (21.6)	1351.0(19.3)	0.055

[a] 1–3 years includes 13–36 months; 3–6 years includes 14–72 months; 6–12 years includes 73–144 months; 12–18 years includes 145–216 months.
[b] Underlying health risk includes stridor when awake, large tongue, micrognathia, preexisting neurologic impairment, history of sleep apnea and snoring, gastroesophageal reflux, chronic constipation, or vomiting. DEX, dexmedetomidine; DEX-CH, dexmedetomidine and chloral hydrate combination; SMD, standardized mean difference; IPTW, inverse probability of treatment weighting.

with propensity score matching and inverse probability of treatment weighting yielded similar results.

5. Discussion

In our cohort, we found that both intranasal high-dose DEX and low-dose DEX-CH combination sedation could achieve a high sedation success rate and had a low incidence of adverse events in children undergoing EEG. There was no significant difference in the onset time between the two groups, and the recovery time was slightly longer in the DEX-CH group.

The success rate of the initial dose of 3 μg/kg DEX was 97.4 % significantly higher than 2.5 μg/kg DEX which the success rate of 87.0 % concluded in our previous published retrospective observational study [15]. Some literature had reported that intranasal DEX was an effective and safe method for sedation, but most of the recommended doses were less than 3 μg/kg [16,17]. Our study proved

Table 2
Associations between sedation protocols and successful sedation or sedation -related complication in the unadjusted analysis, propensity score-matched analysis, and IPTW analysis. *P-value from unadjusted or matched binary regressions models. CI, confidence interval; RR, relative risk.

	DEX n (%)	DEX-CH n (%)	Unadjusted		PSM		IPTW	
			RR (95 % CI)	P-value*	RR (95 % CI)	P-value*	RR (95 % CI)	P-value*
Successful sedation	824 (97.4)	5971(97.5)	0.99(0.98, 1.01)	0.797	0.99(0.98, 1.01)	0.522	0.99(0.99, 1.00)	0.686
Adverse event	16(1.9)	102(1.7)	1.15(0.68, 1.93)	0.322	0.57(0.31, 1.05)	0.071	1.22(0.96, 1.55)	0.100
Bradycardia	13(1.5)	2(0.03)	47.03(10.63, 208.04)	<0.001	13.00(1.71, 99.15)	0.013	48.58(12.43, 189.87)	<0.001
Vomiting	0(0.00)	95(1.6)	0.04(0.002, 0.60)	0.020	0.02(0.00,0.33)	0.006	0.005(0.00, 0.07)	<0.001
Oxygen desaturation	1(0.12)	2(0.03)	3.62(0.33, 39.85)	0.294	0.50(0.05, 5.50)	0.571	2.26(0.67, 7.68)	0.190
Partial airway obstruction	2(0.24)	3(0.05)	4.82(0.81, 28.83)	0.221	2.00(0.18, 22.01)	0.571	2.64(0.32, 25.89)	0.389

Table 3
Associations between sedation protocols and induction time and recovery time in the unadjusted analysis, propensity score-matched analysis, and IPTW analysis. *P-value from unadjusted or matched linear regressions models. IQR, interquartile range.

	unadjusted			PSM			IPTW		
	DEX [median (IQR)]	DEX-CH [median(IQR)]	P-value*	DEX [median (IQR)]	DEX-CH [median(IQR)]	P-value*	DEX [median (IQR)]	DEX-CH [median(IQR)]	P-value*
Redation onset time	19(17, 23)	20(17, 23)	0.088	19(17, 23)	19(17, 23)	0.386	19(17, 23)	20(17, 23)	0.587
Recovery time	46(35, 58)	48(37, 62)	0.003	46(35, 58)	48(41, 61)	<0.001	46(35, 57)	48(37, 62)	0.003

that intranasal 3 μg/kg DEX was a safe sedation method but may lead to a low incidence (1.54 %) of bradycardia. Chrysostomou C et al. found that DEX could slow the heart rate of children with congenital heart disease [18]. In our cases with bradycardia, 5 cases received atropine and 8 cases did not receive medical intervention. We recommend that for children undergoing EEG who depend on heart rate to maintain cardiac output, it is best to use DEX-CH sedation, which has a lower incidence of bradycardia compared to intranasal DEX alone.

Regarding other adverse effects such as oxygen desaturation and vomiting in intranasal DEX group, our findings are consistent with Yang Fei and colleagues, who reported no respiratory-related severe adverse events (such as laryngospasm and bronchospasm) while using intranasal DEX alone [19]. On the other hand, no children experienced vomiting in intranasal DEX group, which contradicts the findings of Hang Chen, who reported vomiting was the most common adverse event [15]. We concluded the possible reason for this discrepancy was the differences in drug administration by nurse anesthetists. Excessive crying may cause aerophagia, which results in flatulence, abdominal distention and vomiting. Therefore, intranasal DEX alone is a simple way, and experienced nurses can quickly complete nasal administration without causing discomfort and crying to the children.

CH is one of the most frequently administered sedative drugs in children. The recommended dosage for use alone is 40–100 mg/kg [6]. But, it has not been effective by using alone in some children, even at the maximum dose. Razieh Fallah had recommended a combination of CH in the lowest dose and antihistamines is safer and more effective for sedation during EEG procedures in children [12]. To achieve a stable sedative effect and reduce adverse events from high doses, most of anesthetists prefer oral CH (30 mg/kg) in combination with intranasal DEX (2 μg/kg) in our center. In our cohort, vomiting (1.55 %) was the most common adverse event, which was self-relief after rest in the DEX-CH group. But the incidence of vomiting was much lower than Dianne G. Valenzuela's study which CH was used alone [20]. DEX-CH sedation increased the success rate of sedation and reduced the adverse effects compared to oral CH alone.

In addition, this study has several limitations. First, vital signs and sedation depth were not continuously monitored during the examination, so the record of onset time and recovery time of sedation may be delayed. Second, our study is retrospective. Continuous blood pressure monitoring was not performed in our center, so we cannot report whether the children had hypertension or hypotension as a possible adverse effect during the whole examination process, which also needs to be confirmed by prospective studies. Third, we did not analyze the relationship between the two methods and EEG results.

6. Conclusion

According to our study, we found both methods for EEG had high sedation success rate and low incidence of adverse events. High-dose intranasal DEX was more likely to induce bradycardia and had a shorter recovery time than the DEX-CH sedation, which was more likely to induce vomiting.

Ethics declarations

This study was reviewed and approved by the Ethics Committee of the Children's Hospital affiliated with Chongqing Medical University, Chongqing, China (Chairperson Hongmei Xu) with the approval number: No. ((2024) Year Aaron trial (research) No.3), dated May 4, 2024.

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Data availability statement

Data associated with this study has not been deposited into a publicly available repository. However, all relevant and pertinent data to support this study is included in the article. Meanwhile, the data used and analysed during the current study available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Liang Wang: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Hezhi Wang:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Wen Tang:** Supervision, Investigation. **Linlin Tang:** Formal analysis, Data curation. **Ying Xu:** Supervision, Investigation. **Ling Xiong:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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