Original Article

อุบัติการณ์และการพยากรณ์การเกิดภาวะกระวนกระวายหลังดมยาสลบในผู้ป่วยเด็กที่ได้รับยาคลอรัลไฮเดรต

งามจิตร์ ภัทรวิทย์*
อรรัตน์ กาญจนวนิชกุล
ธิดา เอื้อกฤดาธิการ
ศรันยู ถิ่นจะนะ

Incidence and Predictors of Emergence Agitation in Pediatric Patients Who Received Chloral Hydrate for Premedication.

Ngamjit Pattaravit, Orarat Karnjanawanichkul, Thida Uakritdathikarn, Sarunyu Thinchana
Department of Anesthesiology, Faculty of Medicine, Prince of Songkhla University, Hat Yai, Songkhla, 90110, Thailand
*E-mail: ngamjitp@yahoo.com
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บทคัดย่อ:

ภาวะกระวนกระวายหลังได้รับยาดมสลบแบบทั้งตัวในเด็กพบได้บ่อยและหายได้เอง ผู้ป่วยจะมีอาการกระสับกระส่าย ไม่ให้ความร่วมมือ ร้องกวน เป็นต้น ในบางกรณีอาจทำให้เกิดอันตรายต่อผู้ป่วยได้

วัตถุประสงค์: เพื่อศึกษาอุบัติการณ์และพยากรณ์การเกิดภาวะกระวนกระวายในผู้ป่วยเด็กหลังได้รับดมยาสลบแบบทั้งตัวที่ได้รับยาคลอรัลไฮเดรต

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบไปข้างหน้า โดยทำการเก็บข้อมูลในผู้ป่วยเด็ก 137 ราย อายุ 2-9 ปี ที่ได้รับยาคลอรัลไฮเดรตก่อนดมสลบ ข้อมูลทั่วไป และพฤติกรรมขณะแยกจากผู้ปกครองจะถูกประเมินก่อนการผ่าตัด หลังการผ่าตัด ผู้ป่วยจะได้รับการประเมินภาวะกระวนกระวายหลังได้รับยาดมสลบแบบทั้งตัวโดยวิสัญญีพยาบาลประจำห้องพักฟื้น

ผลการศึกษา: ผู้ป่วย 47 ราย เกิดภาวะกระวนกระวายหลังได้รับยาดมสลบแบบทั้งตัว พบว่าอุบัติการณ์ของการเกิดภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัวลดลงในผู้ป่วยกลุ่มที่มีการผ่าตัดมาก่อน (adjusted OR=0.43, 95% CI=0.18, 1) และกลุ่มผู้ป่วยที่มีระดับความกระวนกระวายขณะแยกจากผู้ปกครองน้อย (adjusted

ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ อ.หาดใหญ่ จ.สงขลา 90110
รับต้นฉบับวันที่ 12 เมษายน 2553 รับลงตีพิมพ์วันที่ 5 ตุลาคม 2553

OR=0.22, 95% CI=0.07, 0.74) ในขณะที่ผู้ป่วยที่ระยะเวลาฟื้นตัวอยู่ในช่วง 6-10 นาทีหลังหยุดการให้ยาระงับความรู้สึกมีโอกาสเกิดภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกมากกว่าผู้ป่วยที่ระยะเวลาฟื้นตัวอยู่ในช่วง 0-5 นาทีหลังหยุดการให้ยาระงับความรู้สึก (adjusted OR=3.05, 95% CI=1.25, 7.43)

สรุป: อุบัติการณ์การเกิดภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัวเท่ากับร้อยละ 34.3 ประวัติการผ่าตัด พฤติกรรมขณะแยกจากผู้ปกครอง และระยะเวลาฟื้นตัว มีความสัมพันธ์กับการเกิดภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัว

คำสำคัญ: คลอรัลไฮเดรต, ผู้ป่วยเด็ก, ภาวะกระวนกระวายหลังได้รับยาระงับความรู้สึกแบบทั้งตัว

Abstract:

Background: Emergence agitation (EA) is a common self limiting problem after recovery from general anesthesia (GA). Patients with EA will be inconsolable, irritable, uncooperative and may thrash or cry. In some cases EA symptoms can be severe leading to physical harm in children.

Objective: To study the incidence and predictors of EA in pediatric patients who received chloral hydrate for premedication.

Materials and methods: A prospective observational study was conducted on 137 patients aged between 2-9 years who received chloral hydrate for premedication. Demographic data and the child's behavior while separated from their parents were evaluated. After emerging from anesthesia, the child's behaviors were observed by attending nurses.

Results: Forty-seven patients exhibited EA (34.3%). Multivariate analysis showed that children who had a previous history of surgery (adjusted OR=0.43, 95% CI=0.18, 1) tended to have less incidence of EA. Children who were in the slightly anxious tearful subgroup (adjusted OR=0.22, 95% CI=0.07, 0.74) tended to have a lower incidence of EA than the calm cooperative subgroup. Children who woke up 6-10 minutes after the anesthesia was stopped (adjusted OR=3.05, 95% CI=1.25, 7.43) tended to have a higher incidence of EA than children who woke up 0-5 minutes after anesthesia was stopped.

Conclusion: The incidence of EA in pediatric patients who received chloral hydrate was 34.3%. Previous history of surgery, difficulty in separating the patient from the parent and timing to recovery were the predictors of EA.

Key words: chloral hydrate, emergence agitation, pediatric patient

Introduction

Emergence agitation (EA) is a common problem after recovery from general anesthesia (GA). Patients with EA usually have a dissociated state of a consciousness. Children who have EA can be inconsolable, irritable, uncooperative, and may thrash, cry, moan or be incoherent.[1,2] This phenomenon is generally self-limiting within 5-15 minutes.[3]

The overall incidence of EA in postoperative patients is 5.3%[3] and frequently occurs in children, especially in preschool ages.[4-7] Saringcarinkul, et al.[4] reported the incidence of EA in Thai pediatric patients aged between 2-9 years is 43.2%. Previous studies have identified many risk factors of EA in pediatric patients after GA. These include volatile anesthetic drugs, such as sevoflurane and isoflurane, surgical procedures, especially ophthalmic and otological surgery, and the administration of intravenous drugs such as thiopental, propofol, midazolam, remifentanyl, ketamine, droperidol, atropine and scopolamine. [8-12]

There have been studies investigating methods to reduce the incidence of EA, such as using premedication or narcotic drugs. One study found that midazolam and clonidine premedication reduced the incidence of EA when compared with a placebo.[13] However, one study found that midazolam premedication did not reduce the incidence of EA.[14] Viitanen, et al.[15] found that midazolam premedication delayed the recovery period from general anesthesia in children aged 1-3 years, but the reduced incidence of EA may have been due to slower awakening rather than reduced anxiety.

Wheeler, et al.[16] demonstrated that chloral hydrate sedation provided a deeper level of sedation than midazolam in children undergoing echocardiography. In Songklanagarind Hospital, chloral hydrate is the standard premedication drug for pediatric patients who undergo surgery. Standard premedication doses range from 50-75 mg/kg. The peak onset of sedation is 30 minutes after administration. Chloral hydrate is well absorbed in the gastro-intestinal tract and excreted via bile, feces and urine. The duration of effect is 4-8 hours and the elimination half-time is 8-10 hours in plasma. Repeat doses can be administered every 30 minutes and the limitation of dosage is 100 mg/kg.[17,18] However, Malviya et al.[19] reported that agitation is the one of the adverse events after using chloral hydrate for sedation in children undergoing magnetic resonance imaging (MRI) study. The purpose of this study was to examine the incidence of EA in pediatric patients who received chloral hydrate premedication before GA and to identify predictors of EA.

Materials and methods

After being approved by the Ethics Committee, a prospective observational study was done in Songklanagarind Hospital. One hundred and thirty-seven patients aged between 2-9 years old who were scheduled for elective surgery under general anesthesia (GA) and were to receive chloral hydrate 50 mg/kg for premedication were enrolled. The study was conducted from December 2008 to July 2009. Before surgery, the demographic data and history of any previous surgeries were recorded. The child's behavior during separation from their parents was evaluated by an attending anesthesiologist using a three-point scale in which 1=calm/cooperative, 2=slightly anxious/tearful, and 3=agitated/non-cooperative.[6] Anesthetic medications, technique, duration of anesthesia and time to recovery were recorded by an attending anesthetic nurse. Standard treatment for general anesthesia was provided for all patients.

At the post anesthetic care unit (PACU), emergence behaviors were observed by attending PACU nurses. After arrival in the PACU, the

presence or absence of EA was assessed using the emergence agitation scale (EA) -0=localized or complained of pain, 1=obtunded with no response to stimulation, 2=asleep but responsive to movement or stimulation, 3=awake and responsive, 4=crying and 5=thrashing behavior requiring restraint.[20] Emergence score ranging from 0-3 indicates absence of EA and between 4-5 indicates presence EA. The duration of EA and any pharmacologic and non-pharmacologic intervention were recorded if EA was present.

The required sample size was determined according to a previous study which found that the incidence of EA in Thai pediatric patients aged between 2-9 years old was 43.2%.[4] A sample size of 137 patients was determined (precision, 0.085; CI 95%). A statistical power of this study was 80%. A p-value < 0.05 was considered to indicate statistical significance. All data were analyzed by R program version 2.8.2. Categorical data were presented as frequency (percent). Pearson chi-square test and fisher exact test were used for univariate analysis. From univariate analysis age, which was expected to be the strongest predictor, and other variables which had a p-value < 0.2 were analyzed by multivariate analytic logistic regression to determine the predictors of EA.

Results

One hundred and thirty-seven subjects were enrolled in this study. Demographic data and characteristics of each study group are shown in Table 1. There were 47 patients (34.3%) who exhibited EA with the highest occurrence 0-5 minutes after ceasing anesthesia. There were 2 patients who exhibited EA symptoms longer than 25 minutes, but did not cause a delay in discharge from the PACU. 43 patients (85.1%) who had EA were treated by intravenous fentanyl and psychological support, while the other 4 (14.9%) were able to be calmed down using only psychological support and parental presentation.

The incidence of EA related to perioperative factors are shown in Table 2. Children who underwent ophthalmic surgery had the highest incidence of EA (47.4%), while children who underwent other types of surgery: otologic, urologic, orthopedic or other, had incidences of EA 26.1%, 22.2%, 35.3% and 27.3%, respectively. The incidence of EA in children who received propofol, thiopenthal and sevoflurane for induction were 60.0%, 27.7% and 38.8%, respectively. Children who received intravenous drugs for induction and sevoflurane for maintenance had a higher incidence of EA (47.4%) than children who received another anesthetic technique. Children who received fentanyl for analgesia had a higher incidence of EA (36.8%) than children who received intravenous morphine or caudal anesthesia combined with intravenous narcotic drug. Children who underwent GA for 31-60 minutes had a higher incidence of EA (48.3%) than children who underwent GA less than 31 minutes and more than 60 minutes. The incidence of EA in the children who woke up after ceasing anesthesia 0-5 minutes, 6-10 minutes, 11-15 minutes and more than 15 minutes were 51.1%, 27.9%, 22.2% and 6.4%; respectively.

Predictors of EA are shown in Table 3. Five variables from univariate analysis, previous

surgical history, difficult to separate from parent, induction agents, duration of anesthesia and time to recovery, which p-values < 0.2 and age variable were subsequently analyzed by multivariate analysis. Previous surgical history and difficulty separating from parent were found to be negative predictors of EA with p-values of 0.047 and 0.030 respectively while awakening time was found to be positive predictor of EA with p-value 0.042.

Multivariate analysis was performed on these three variables. Children who had a previous surgical history had a lower odd of EA than those with no history (adjusted OR=0.43, 95% CI=0.18, 1, p-value=0.047). Children who were slightly anxious and tearful had less odd of EA than calm and cooperative children (adjusted OR=0.22, 95% CI=0.07, 0.74, p-value=0.015) while no statistical significance was found in agitated non-cooperative children (adjusted OR=0.39, 95% CI=0.09, 1.69, p-value=0.206). Children who woke up 6-10 minutes after the ceasing anesthesia had a higher odd of EA than the children who woke up 0-5 minutes after ceasing anesthesia (adjusted OR=3.05, 95% CI= 1.25, 7.43, p-value=0.041). There was no statistical significance in the group of children who woke up 11-15 minutes and longer than 16 minutes after ceasing anesthesia (adjusted OR=3.67 and 3.52, 95% CI =0.92, 14.66 and 0.72, 17.3, p-value= 0.065 and 0.121).

Table 1 Demographic data and sample characteristics

Patient characteristics	EA, n (%)		Total, n (%)
	Yes	No	
Sex			
Female	25 (36.2)	44 (48.9)	69 (51.4)
Male	22 (32.4)	46 (67.6)	68 (49.6)
Age group (yr)			
6-9	15 (28.8)	37 (71.2)	52 (38.0)
2-5	32 (37.6)	53 (62.4)	85 (62.0)
Previous surgery			
No	29 (43.3)	38 (56.7)	67 (48.9)
Yes	18 (25.7)	52 (57.8)	70 (51.1)
Separation state			
Calm/cooperative	33 (30.3)	76 (69.7)	109 (79.6)
Slightly anxious/tearful	9 (60.0)	6 (40.0)	15 (10.9)
Agitated/non-cooperative	5 (38.5)	8 (61.5)	13 (9.5)

EA = Emergence agitation

Table 2 Incidence of emergence agitation related to perioperative factors

Variable	EA, n (%)		Total, n (%)
	Yes	No	
Type of operation			
Ophthalmic surgery	18 (47.4)	20 (52.6)	38 (27.7)
Otological surgery	6 (26.1)	17 (73.9)	23 (16.8)
Urology surgery	2 (22.2)	7 (77.8)	9 (6.6)
Orthopedic surgery	12 (35.3)	22 (64.7)	34 (24.8)
Other surgery	9 (27.3)	24 (72.7)	33 (24.1)
Induction drug			
Propofol	3 (60.0)	2 (40.0)	5 (3.7)
Thiopenthal	18 (27.7)	47 (72.3)	65 (47.4)
Sevoflurane	26 (38.8)	41 (61.2)	67 (48.9)
Anesthetic technique			
Sevoflurane induction and balance anesthesia	15 (33.3)	30 (66.7)	45 (32.8)
Sevoflurane induction and maintenance	9 (37.5)	15 (62.5)	24 (17.5)
IV induction and sevoflurane maintenance	9 (47.4)	10 (52.6)	19 (13.9)
IV induction and balance anesthesia	14 (28.6)	35 (71.4)	49 (35.8)
Narcotic			
Morphine	2 (22.2)	7 (77.8)	9 (6.6)
Fentanyl	42 (36.8)	72 (63.2)	114 (83.2)
Caudal block	1 (20.0)	4 (8.0)	5 (3.6)
Caudal block plus IV narcotic	2 (22.2)	7 (77.8)	9 (6.6)
Duration of anesthesia (min)			
0-30	1 (11.1)	8 (88.9)	9 (6.6)
31-60	14 (48.3)	15 (51.7)	29 (21.1)
61-90	13 (30.2)	30 (69.8)	43 (31.4)
91-120	12 (41.4)	17 (58.6)	29 (21.1)
>120	7 (25.9)	20 (74.1)	27 (19.8)
Speed of recovery (min)			
0-5	23 (51.1)	22 (48.9)	45 (32.9)
6-10	17 (27.9)	44 (72.1)	61 (44.5)
11-15	4 (22.2)	14 (77.8)	18 (13.1)
≥16	3 (6.4)	10 (11.1)	13 (9.5)

EA = Emergence agitation

Table 3 Predictors of emergence agitation

Variables	Crude OR (95%CI)	P-value*	Adjusted OR (95%CI)	P-value**
Sex				
Female	1	0.766		
Male	0.84 (0.42, 1.71)			
Age group (yr)				
6-9	1	0.386	1	0.557
2-5	1.49 (0.71, 3.13)		1.30 (0.54, 3.10)	
Previous surgery				
No	1	0.047	1	0.047†
Yes	0.45 (0.22, 0.93)		0.43 (0.18, 1.00)	
Separation difficulty				
Calm/cooperative	1	0.073	1	0.030†
Slightly anxious/tearful	0.29 (0.1, 0.88)		0.22 (0.07, 0.74)	
Agitated/uncooperated	0.69 (0.21, 2.28)		0.39 (0.09, 1.69)	
Type of operation				
Ophthalmic surgery	1	0.333		
Otologic surgery	2.55 (0.83, 7.88)			
Urologic surgery	3.15 (0.58, 17.17)			
Orthopedic surgery	1.65 (0.64, 4.26)			
Other surgery	2.40 (0.89, 6.5)			
Induction				
Propofol	1	0.169	1	0.265
Thiopenthal	3.92 (0.06, 25.41)		4.20 (0.56, 31.73)	
Sevoflurane	2.37 (0.37, 15.13)		2.55 (0.35, 18.42)	
Technique				
Inhalation induction and balance anesthesia	1	0.505		
Inhalation induction and maintenance	0.83 (0.3, 2.34)			
IV induction and inhalation maintenance	0.56 (0.19, 1.66)			
IV induction and balance anesthesia	1.25 (0.52, 3)			
Narcotic				
Morphine	1	0.666		
Fentanyl	0.49 (0.1, 2.47)			
Caudal anesthesia	1.14 (0.08, 16.95)			
Other	1 (0.11, 9.23)			
Duration of anesthesia (min)				
0-30	1	0.184		
31-60	0.13 (0.01, 1.21)			
61-90	0.29 (0.03, 2.55)			
91-120	0.18 (0.02, 1.61)			
>120	0.36 (0.04, 3.39)			

Table 3 (Continued)

Variables	Crude OR (95%CI)	P-value*	Adjusted OR (95%CI)	P-value**
Speed of recovery (min)				
0-5	1	0.041	1	0.042†
6-10	2.71 (1.2, 6.08)		3.05 (1.25, 7.43)	
11-15	3.66 (1.04, 12.84)		3.67 (0.92, 14.66)	
≥16	3.48 (0.85, 14.37)		3.52 (0.72, 17.30)	

EA = Emergence agitation, *P-value from univariate analysis, **P-value from multivarite analysis with logistic regression, † = Statistically significant

Discussion

The incidence of EA in this study was 34.3% with the highest occurrence in children whose time to recovery was between 5 and 10 minutes. The incidence of EA in our results was lower than a previous study of Thai pediatric population by Saringcarinkul, et al.[4] (43.2%) which children who received chloral hydrate had a higher incidence (55.8%). Individual premedication protocol in each hospital such as the type of drugs, timing to administer the drug and difference research protocols might have an effect on the incidence of EA.

Several studies reported that the age variable was a predictor of EA.[4-7] These studies were done in various ranges of age group, such as the study by Aono, et al.[5] which done in pediatric patient aged between 3 and 5 years and the study by Voepel-Lewis, et al.[6] which done in pediatric patient aged between 3 and 7 years. Our study found that age variable was not a predictor of EA (p-value 0.386). This result was not consistent with this previous studies.[4,5] Our explanation for this finding is that the age variable in our study was divided into two groups (2-5 years and 6-9 years) and was collected in term of categorical data. So the age group in our study included both the significant and non-significant ages. This could have effected to the results.

Children who had a previous history of surgery tended to have a lower incidence of EA than those with no such history. (adjusted OR=0.43, 95% CI=0.18, 1, p-value=0.047). This was consistent with the report by Voepel-Lewis, et al.[6] Children who have a previous history of surgery have more experience with strangers and the operating room, and are familiar with the sequences of anesthesia and PACU care, which would naturally tend to reduce anxiety and EA.

Saringcarinkul, et al.[4] reported that children who were difficult to separate from their parent were more likely to experience EA than children who were easily separated, however this report was not compatible with our finding (p-value 0.047). Our study showed that children who were

in the slightly anxious tearful subgroup had a lower incidence of EA than the calm cooperative subgroup (adjusted OR=0.22, 95% CI =0.07, 0.74, p-value=0.015). In this study, the calm cooperative group included not only the children who were cooperative and adapted themselves well to the new environment but also the children who were asleep and thus did not adapt themselves to the new environment before anesthesia. After waking up from anesthesia, the children who were asleep before the anesthesia were more anxious than the children who were in the slightly anxious tearful group and who had already adapted themselves. This finding would indicated that parents should be permitted to look after their children as soon as they arrive in the PACU to help their children adapt themselves, which would reduce anxiety and EA.

Previous studies have found that volatile anesthetic drugs, such as sevoflurane, were one of the predictors of EA, because of their lower solubility in blood which results in rapid awakening from anesthesia.[6,21] In this study, there was no statistically significant association found between induction and anesthetic techniques and the incidence of EA. We expected to find that children who had rapid emergence would have a higher incidence than those with a slower emergence but instead we found that the children who woke up during 6-10 minute after ceasing anesthesia tended to have a higher incidence of EA than children who woke up earlier (adjusted OR=3.05, 95% CI= 1.25, 7.43, p-value=0.014). This finding was contrary to earlier reports by Aono, et al. and Uezono, et al.[5,21] Our explanation for this finding is that differences in techniques among the anesthesia trainees could effected the results of the study. We found that some patients who woke up 0-5 minutes after ceasing anesthesia did not have full consciousness when were extubated. They may have had some residual anesthetic agent that would make them continue sleeping in the PACU. This could have resulted in a lower incidence of EA than might have been found if the techniques were more rigorous, as experienced anesthesiologists would provide.

This study had some limitations. First, some numerical data were recorded as categorical data so we could not exactly define values such as age and time to awakening in our report. Second, EA can be difficult to evaluate, and sometimes cannot be distinguished from other causes of anxiety, such as pain or separation anxiety in young children, so the reported incidence of EA may be overestimated. Further well-designed randomized controlled trials (RCT) should be performed to control these and other potential confounding factors.

Conclusion

This study found that the incidence of EA in pediatric patients who received chloral hydrate before GA was 34.3%. Previous history of surgery, difficulty to separate the patient from the parent were the negative predictive factors of EA while awakening time between 6-10 minutes after GA was the positive predictive factors of EA.

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