AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

OTO Open
2024, Vol. 8(4):e70023

DOI: 10.1002/oto2.70023
http://oto-open.org
WILEY

Efficacy of Rectal Versus Oral Chloral Hydrate in Pediatric Auditory Brainstem Response: Randomized Controlled Trial

Chutaporn Siripermpool, BPharm[1], Nalinee Pattrakornkul, MD[2], Thanitda Thongsattra, BNS[3], and Narit Jianbunjongkit, MD[4]

Abstract

Objective. To compare sedation success rates between rectal (RCH) and oral chloral hydrate (OCH) administration in children undergoing auditory brainstem response (ABR) testing and assess the incidence of adverse effects.

Study Design. Randomized controlled trial, performed between May 2023 and August 2023.

Setting. Ear, Nose, and Throat Outpatient Department at tertiary care hospital.

Methods. Pediatric patients aged 1 to 5 years, who were indicated for ABR testing were enrolled and randomly divided into 2 groups. The control group received 10% wt/vol chloral hydrate orally at a dose of 50 mg/kg, while the other group received the same dose through rectal administration. Onset of sedation, duration of sedation, recovery time, vital signs, and adverse effects were recorded and analyzed to assess sedative effectiveness and safety.

Results. Eighty-eight children were randomly assigned to RCH or OCH administration groups, the sedation success rates of RCH and OCH groups were 84.09% and 90.91%, respectively ($P = .33$). Adverse effects were detected in 11 children (12.5%), with a vomiting rate of 20.45% in the oral group versus 0% in the rectal group ($P = .002$). The diarrhea rate was 4.55% in the rectal group versus 0% in the oral group ($P = .16$). In either group, no serious adverse effects were documented.

Conclusion. RCH and OCH are both safe and effective for short-term sedation in pediatric patients during ABR testing. Interestingly, RCH administration offers a high success rate without vomiting or major adverse effects. This study established the effectiveness of RCH for sedation in children under specialized supervision.

Keywords

auditory brainstem response, choral hydrate, rectal administration, sedation

Received August 21, 2024; accepted September 14, 2024.

At present, hearing tests are conducted in young children to detect any abnormalities that may affect their language development. The auditory brainstem response (ABR) test, which is a gold standard, is employed to assess hearing status owing to its high specificity and precision, allowing for a neurophysiological evaluation of the auditory pathways from the inner ear to the upper brainstem.[1-3] Before the test, sedative medication is administered to ensure participation, minimize procedural artifacts, and achieve a moderate sedation level. This guarantees that the child remains asleep throughout the procedure, facilitating a more efficient examination.

Chloral hydrate, a nonopioid and nonbenzodiazepine hypnotic, is commonly used in uncooperative children as a sedative for painless procedures, such as magnetic resonance imaging,[4-7] computed tomography,[5-8] electroencephalography,[9,10] echocardiography,[11-13] dental,[14,15] and ophthalmic procedures,[16-18] and ABR test.[19-26] It can be administered orally or rectally to children below 6 years old.[26,27] Chloral hydrate has a strong and bitter taste, potentially causing nausea and vomiting by stimulating the upper gastrointestinal tract.[11] Recent studies on orally administered chloral hydrate for short-term sedation during the ABR test reported success rates ranging from 56.1% to 100%, with indicated adverse reactions such as vomiting, apnea, rash, and prolonged sedation.[19-24]

In Thailand, chloral hydrate is not included in any commercially available pharmaceutical products.

[1]Department of Pharmacy, Burapha University Hospital, Faculty of Medicine, Burapha University, Chonburi, Thailand
[2]Department of Pediatrics, Faculty of Medicine, Burapha University, Chonburi, Thailand
[3]Out Patient Department of Ear Nose and Throat, Faculty of Medicine, Burapha University, Chonburi, Thailand
[4]Department of Otorhinolaryngology, Faculty of Medicine, Burapha University, Chonburi, Thailand

Corresponding Author:
Narit Jianbunjongkit, MD, Department of Otorhinolaryngology, Faculty of Medicine, Burapha University, 169/382 Longhadbangsaen Road, Sansuk Subdistrict, Mueang District, Chonburi 20131, Thailand.
Email: naritj@buu.ac.th

Therefore, hospital pharmacists must prepare the compound extemporaneously to meet the personalized needs of patients and ensure compliance with clinical treatment guidelines.

Extemporaneous compounding formulations consist of active pharmaceutical ingredients and excipients. The active pharmaceutical ingredient is a major component that provides pharmacological activity in the treatment, prevention, and diagnosis of disease or affecting any function of the body. Meanwhile, excipients serve as the vehicles and diluents for the pharmaceutical ingredient.[28,29] Despite the development of formulation using flavored syrup and sweetening agents to mask the taste, it remains ineffective and leads to children being uncooperative with administration. Considering this problem, chloral hydrate rectal solution is used to facilitate easier administration in children.

However, research on rectally administered chloral hydrate in the ABR test is limited. Therefore, this study aimed to compare the sedation success rates between rectal and oral administrations of chloral hydrate in children undergoing the ABR test and to assess the incidence of adverse effects.

Methods

Study Design and Setting

This prospective randomized controlled trial was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Burapha University (Approval Number: HS107/2565). After explanation of the protocol, the parents signed the informed consent form.

Preparation of the Study Medications

In Thailand, chloral hydrate solution is currently unavailable commercially. A pharmacist prepared rectal and oral formulations at a concentration of 100 mg/mL using an extemporaneous method. Both formulations contain chloral hydrate powder (S. Tong Chemicals) as the active ingredient. The rectal formulation improves solubility with polyethylene glycol (PEG) 400 (S. Tong Chemicals), whereas the oral formulation contains simple syrup (Vidhyasom) as sweetening agent and paraben concentrate as preservative. The preparation was stored in an amber glass bottle in the refrigerator (2-8°C) and is stable for 90 days.

Sample Size Calculation

The study compared the sedation success rates for the ABR test in children by evaluating the proportion differences between the rectal and oral administration groups. Prior to this study (conducted in 2023), there was no available data on the sedation success rate of rectal chloral hydrate (RCH) compared with oral chloral hydrate (OCH) in children undergoing the ABR test. The sample size calculation relied on a previous study.[8] A power analysis was conducted using Minitab® to determine the minimum sample size required to test the study hypothesis, considering the sedation success rates of RCH ($p_1 = 0.9610$) and OCH ($p_2 = 0.8108$) as reported by Nie et al. It was assumed that the sedation success rate was higher in the rectal administration group than in the oral group (with a significance level of the test set at 0.05 [$\alpha = .05$] and the power of the test at 80% [$\beta = .20$]), with an expected difference in the proportions of 0.20 ($\Delta = 0.20$). To compensate for the dropout rate, the initial sample size of 40 patients per group was increased by 10%, resulting in the final sample size of 44 for each group. In total, 88 participants were enrolled in the study.

Participants

The study included children aged 1 to 5 years who underwent the ARB test between May and August 2023 at the Ear, Nose, and Throat Outpatient Department of Burapha University Hospital, Chonburi, Thailand. An independent nurse performed randomization using a computer-generated list of random numbers, maintaining a 1:1 allocation ratio for the 2 groups. The investigator was blinded to the group allocation. The control group received OCH, and the other group received RCH. The participants, classified as American Society of Anesthesiology class 1, were excluded if they met any of the following criteria: allergy to chloral hydrate, unstable vital signs, airway problems such as obstructive sleep apnea, cardiovascular disease, liver and kidney disease, seizures, or sick on the examination day. The template for the Consolidated Standards of Reporting Trials flow diagram is presented in **Figure 1**.

Intervention

Before the procedure, the children were evaluated by the Ear, Nose, and Throat specialist and asked about their medical history. The obtained data were recorded in the case record form by the research nurses, who then briefed the parents on the procedure, explaining its significance, necessity, risks, benefits, and potential side effects. There patients were queried about the children's medical history, drug allergies, and the research procedures. After explanation of the protocol, the parents signed the informed consent form and were instructed to make sure that their children fasted for at least 2 hours and had defecated before the ABR test.

The research nurse administered RCH using a plastic enema ball. After obtaining the study drug, the nurse lubricated the end tip of the plastic enema ball with lubricating gel, gently inserted it into the rectum, squeezed the drug out, pulled out the enema ball, compressed the children's buttocks toward the anus from both sides, and maintained this position for 5 minutes. Meanwhile, OCH was administered at the same dose of 50 mg/kg using a plastic syringe.

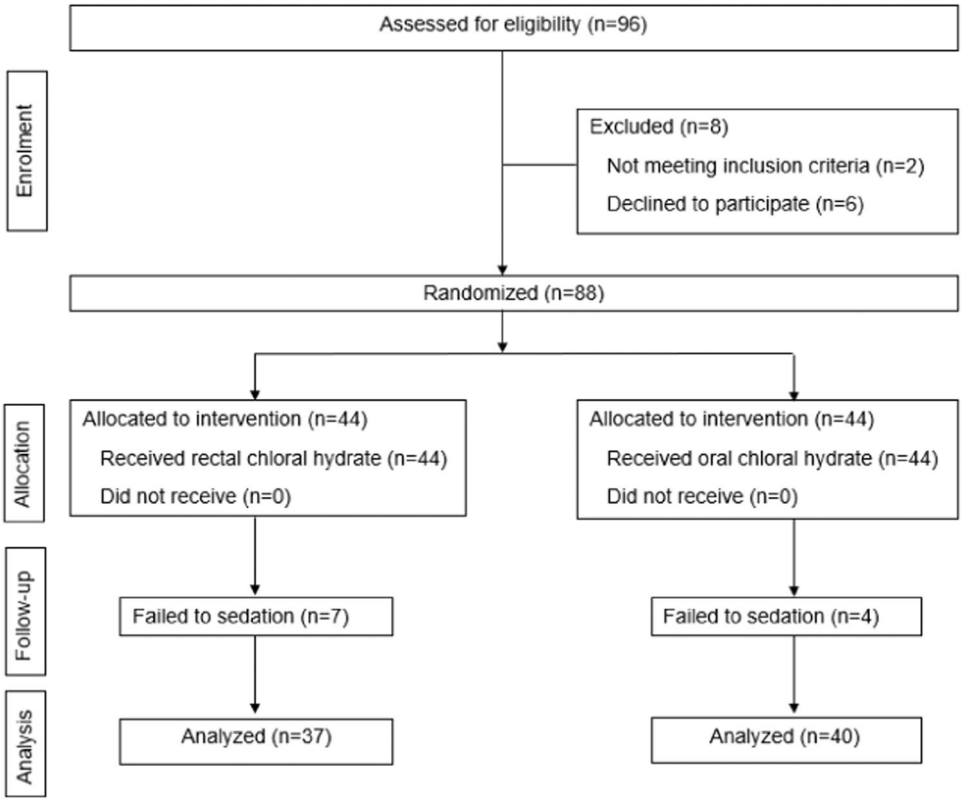

Figure 1. Consolidated Standards of Reporting Trials flowchart showing the enrollment, allocation, follow-up, and data analysis.

Children who did not sleep within 30 minutes, vomit, or defecate after the initial dose received a second dose supplemented at 50 mg/kg body weight, ensuring that the total maximum dose did not exceed 120 mg/kg or 2 g. Each medication was labeled with the study sample number, administration time, and administration date. The pharmacy coded each study drug to maintain investigator blinding.

The sedation scores, assessed using the University of Michigan Sedation Scale,[30] ranged from 0 to 4 (0 = *awake, alert*; 1 = *sleepy, responsive to conversation and/or sounds*; 2 = *sleeping, easily aroused with light tactile stimulation*; 3 = *deep sleep, aroused only with significant physical stimulation*; 4 = *unarousable*). The respiratory rate, pulse rate, and oxygen saturation were recorded before drug administration and monitored at 15-minute intervals for 2 cycles and then every 30 minutes until the children were awake. Adverse effects were recorded during the procedure. In addition, a tank of oxygen, a cannula or mask for oxygen, a suction machine, and a resuscitation equipment were all readily available. If oxygen saturation decreased, a nasal cannula or oxygen mask with 100% oxygen was promptly administered.

After drug administration, the children were placed in a quiet room to sleep. The ABR test was conducted when the sedation score reached 2, and the research nurse noted the sedation onset. The sedation duration was recorded when the score reached 2 and remained above that level. The time from drug administration to discharge of the children after the procedure was recorded as the recovery time. After the completion of the procedure, the children were stimulated to wake up. Those who did not immediately wake up were closely monitored. All children that met the discharge criteria, including being conscious with a sedation score ≤ 1, normal breathing and respiratory rates, oxygen saturation ≥ 95%, and stable vital signs, were allowed to return home.

Statistical Analysis

Statistical analysis was conducted using Minitab® version 21 (Minitab Inc). Categorical variables were expressed as count (n) and percentages (%), whereas continuous variables were expressed as means and standard deviations (mean ± SD). The 2-sample t test was employed to compare the differences between the 2 groups, whereas the paired t test was used to assess the differences in vital signs within the group before to after sedation. Analyzing the rates of successful sedation and adverse events as percentages, a comparison between the groups was performed using the z test statistic for proportion difference. Statistical significance was considered at a $P < .05$.

Results

This study enrolled 96 children, of whom 88 met the inclusion criteria and were randomly divided into 2 groups, namely, RCH and OCH, for the ABR test from May to August 2023 in our hospital. The patients in both

Table 1. Demographic and Baseline Characteristics Among the Groups (n = 88)

Characteristic	RCH (n = 44)	OCH (n = 44)	*P* value
Age, y (mean ± SD)	2.67 ± 0.85	2.52 ± 1.07	.45
Sex, %			.79
Male	35 (79.55)	36 (81.82)	
Female	9 (20.45)	8 (18.18)	
Body weight, kg (mean ± SD)	14.92 ± 2.85	15.12 ± 4.75	.82
Dose of chloral hydrate, mg/kg (mean ± SD)	88.70 ± 20.70	85.60 ± 24.20	.54
Underlying disease, %			
ASD	4 (9.09)	6 (13.64)	.50
ADHD	1 (2.27)	2 (4.55)	.56
G6PD deficiency	2 (4.55)	5 (11.36)	.24
AR	1 (2.27)	0 (0.00)	.33
Hypothyroid	0 (0.00)	1 (2.27)	.33
Current medicine, %			
Risperidone	3 (6.82)	3 (6.82)	1.00
Levothyroxine	0 (0.00)	1 (2.27)	.33
O_2 saturation, %	97.89 ± 1.08	97.34 ± 1.54	.06
Pulse rate, per min	94.93 ± 8.62	98.50 ± 11.50	.10
Respiratory rate, per min	22.70 ± 2.01	23.11 ± 1.97	.34

All *P* values derived from the 2-sample *t* test. $P < .05$ was considered to indicate statistical significance.
Abbreviations: ADHD, attention deficit hyperactivity disorder; AR, allergic rhinitis; ASD, autism spectrum disorder; G6PD, glucose-6-phosphate dehydrogenase; OCH, oral chloral hydrate; RCH, rectal chloral hydrate; SD, standard deviation.

Table 2. Sedation Success Rate and Incidence Rate of Adverse Effects in the Treatment Groups

Outcomes	RCH (n = 44)	OCH (n = 44)	*P* value
Successful sedation, %	37 (84.09)	40 (90.91)	.33
Adverse effects			
Vomiting, %	0 (0.00)	9 (20.45)	.002
Diarrhea, %	2 (4.55)	0 (0.00)	.16

P values were derived using the *z* test statistic for proportion differences. $P < .05$ was considered to indicate statistical significance.
Abbreviations: OCH, oral chloral hydrate; RCH, rectal chloral hydrate.

groups had similar age, sex, weight, dose of chloral hydrate, underlying disease, current medication, and baseline vital signs ($P > .05$) (**Table 1**). All the study participants did not achieve a sedation score greater than 3.

A total of 7 (15.91%) and 4 (9.09%) children in the RCH and OCH groups, respectively, failed to achieve sedation; thus, statistical analyses for successful sedation were conducted on 37 and 40 participants in the 2 groups, respectively. The difference in the rates of successful sedation between the OCH group (90.91%) and the RCH group (84.09%) was not statistically significant ($P = .33$). Adverse effects were observed in 11 children (12.50%), but all of them fully recovered. Nine (20.45%) children in the OCH group experienced vomiting but none in the RCH group ($P = .002$). Furthermore, 2 children (4.55%) in the RCH group had diarrhea but none in the OCH group ($P = .16$) (**Table 2**). No serious adverse effects were observed in our study.

The mean onset time of sedation was 55.50 ± 31.80 minutes in the RCH group versus 48.70 ± 24.40 minutes in the OCH group ($P = .29$). In addition, the mean recovery time was 97.10 ± 29.60 minutes in the RCH group versus 109.40 ± 32.40 minutes in the OCH group ($P = .08$). However, the mean duration of sedation was significantly longer in the OCH group (54.60 ± 24.80 minutes) than in the RCH group (38.60 ± 18.80 miutes) ($P = .002$) (**Figure 2**).

Table 3 presents a comparison of the changes in vital sign before and after sedation in both groups. In the RCH group, the postsedation oxygen saturation was significantly higher than the presedation oxygen saturation (98.22% ± 1.25% vs 97.76% ± 1.12%, respectively, $P = .04$). The pulse rates before and after sedation were 94.89 ± 9.31 and 94.81 ± 9.26 per minute, respectively ($P = .95$). Furthermore, the respiratory rates before and after sedation were 22.73 ± 2.16 and 22.76 ± 2.52 per minute, respectively ($P = .94$). In the OCH group, the presedation respiratory rate was significantly higher than the postsedation rate (22.93 ± 1.89 vs 22.18 ± 1.82 per minute, respectively, $P = .04$). However, the oxygen saturation levels exhibited no significant difference before and after sedation (97.33% ± 1.61% and 97.65% ± 1.17%, respectively; $P = .20$), and likewise, the pulse rate exhibited no significant changes before and after sedation (98.20 ± 11.94 and 97.10 ± 13.25 per minute, respectively; $P = .61$).

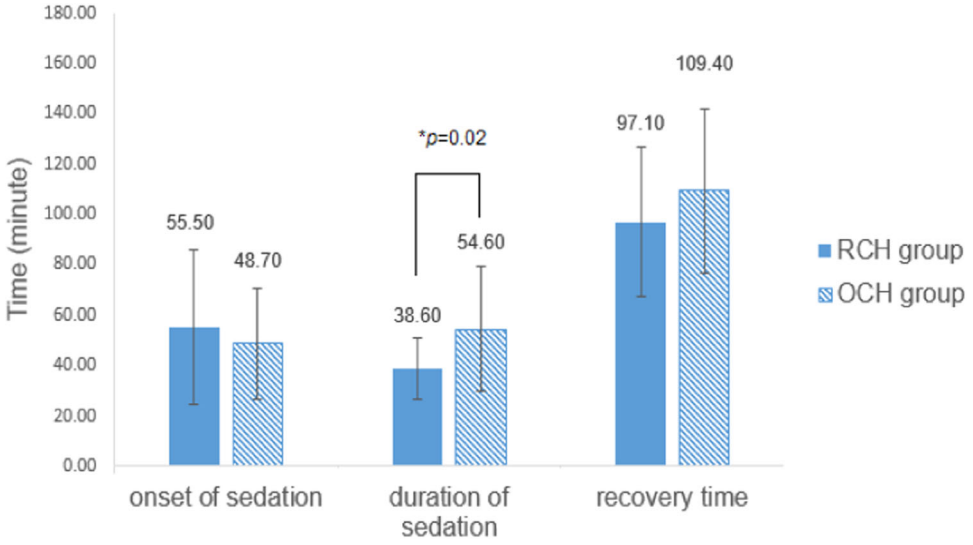

Figure 2. Time to sedation onset and recovery of the treatment groups. OCH, oral chloral hydrate; RCH, rectal chloral hydrate.

Table 3. Changes in Vital Signs From Before to After Sedation of the Treatment Groups

	RCH (n = 37)			OCH (n = 40)		
Parameters	Before sedation	After sedation	*P* value	Before sedation	After sedation	*P* value
O_2 saturation (%)	97.76 ± 1.12	98.22 ± 1.25	.04	97.33 ± 1.61	97.65 ± 1.17	.20
Pulse rate (per minute)	94.89 ± 9.31	94.81 ± 9.26	.95	98.20 ± 11.94	97.10 ± 13.25	.61
Respiratory rate (per minute)	22.73 ± 2.16	22.76 ± 2.52	.94	22.93 ± 1.89	22.18 ± 1.82	.04

P values derived from the paired *t* test. $P < .05$ was considered to indicate statistical significance.
Abbreviations: OCH, oral chloral hydrate; RCH, rectal chloral hydrate.

Discussion

In this randomized controlled trial, the RCH group achieved a slightly lower sedation success rate than the OCH group (84.09% vs 90.91%, respectively), with no statistically significant difference ($P = .33$). The children in the RCH group who failed to achieve sedation expelled the drug after administration, resulting in poor absorption and insufficient drug levels, which led to sedation failure. The success rate varies based on various conditions such as the administration route, procedure type, age, and dose of the sedative drug.

The procedure type significantly influences success rates, with shorter interventions demonstrating higher success rates than longer ones. Furthermore, sedation duration is crucial in determining the success rates. Hijazi et al recommended age-dependent dosing of chloral hydrate, noting correlations with age and body weight.[31] Thus, ensuring sufficient duration of sedation is correlated with achieving high success rates.

Our study found no significant difference in the mean onset time of sedation between the RCH (55.50 ± 31.80 minutes) and OCH (48.70 ± 24.40 minutes) groups ($P = .29$). Similarly, the mean recovery time did not significantly differ between the RCH (97.10 ± 29.60 minutes) and OCH (109.40 ± 32.40 minutes) groups ($P = .08$), which is consistent with our previous findings.[8] However, the OCH group had a significantly longer mean sedation duration than the RCH group (54.60 ± 24.80 vs 38.60 ± 18.80 minutes, respectively, $P = .002$), resulting in a higher success rate that was not statistically significant. While the RCH group exhibited a significant increase in postsedation oxygen saturation compared with the presedation oxygen saturation, this change lacked clinical significance. Similarly, although the presedation respiratory rate was significantly higher than the postsedation rate in the OCH group, the difference was not clinically significant.

Several studies reported shorter mean onset time of sedation than our study, which utilized age-dependent dosing of chloral hydrate. Nie et al observed mean onset times of 18.54 ± 9.99 minutes in the RCH group and 24.83 ± 11.25 minutes in the OCH group, with the children having a mean age of 16.50 months.[8] Similarly, Azizkhani et al obtained mean onset times and durations of 24.50 ± 6.10 versus 12.90 ± 2.80 minutes, respectively, in children aged 2 to 6 years.[32]

The time difference after sedation with different administration routes could be attributed to pharmacokinetic factors, impacting onset, duration, and recovery time. In a bioavailability report by Breimer et al, chloral

hydrate solution with PEG administered rectally achieved a bioavailability of 84%.[33] This is consistent with the report by de Boer et al, suggesting that rectal administration enables rapid absorption, bypassing hepatic metabolism and reducing gastrointestinal irritation and nausea.[34] In our study, diarrhea was reported in only 2 children (4.55%) in the RCH group, all of whom recovered without requiring medical treatment. Meanwhile, the OCH group had a vomiting rate of 20.45%. Previous literature indicates that vomiting is the most common side effect with OCH, with incidence rates ranging from 8.70% to 20.00%.[9,15,19,21] Some serious side effects, such as apnea (0.50%), rash (0.50%), prolonged sedation (0.90%), and oxygen desaturation (2.90%), have also been reported.[19,21,32]

In summary, our study observed a high success rate (84.09%) in the RCH group without serious adverse effects. RCH appears suitable for short-time procedures, whereas OCH is preferable for longer ones. However, RCH offers adequate sedation duration for the ABR test and a quicker recovery compared with OCH. Notably, vomiting occurred in 20.45% of the children in the OCH group but did not occur in the RCH group.

Limitations

This study is limited by the extemporaneous formulation of RCH. First, there is a lack of investigation into pharmacokinetics, such as the metabolite conversion rate to the active metabolite (trichloroethanol) and its half-life. Second, the study duration is short. Future research should explore the pharmacokinetics of RCH and extend the timeframe, which could be beneficial for other painless procedures in children.

Conclusion

Our study confirms the safety and effectiveness of both RCH and OCH for sedation in children undergoing the ABR test. Interestingly, RCH proves its superiority in terms of success rate by significantly reducing adverse effects, particularly vomiting. This suggests that RCH is useful for the ABR test and does not cause serious adverse reactions when administered under specialized supervision.

Acknowledgments

The authors are grateful to the insightful cooperation of staffs of the Outpatient Department of Ear Nose and Throat of Burapha University Hospital, Chonburi, Thailand.

Author Contributions

Chutaporn Siripermpool, conceptualization, study design, data collection, data interpretation, writing, editing, revising manuscript; **Nalinee Pattrakornkul**, study design, critical review manuscript; **Thanitda Thongsattra**, study design, data collection, critical review manuscript; **Narit Jianbunjongkit**, supervision, study design, critical review manuscript.

Disclosures

Competing interests: There is no conflict of interest.

Funding source: This study was funded by Faculty of Medicine, Burapha University, Grant Number 004/2566.

ORCID iD

Narit Jianbunjongkit http://orcid.org/0009-0007-8779-6310

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