Original Article

ประสิทธิผลของไมดาโซแลมผสมไฮดร็อกซีซีนเปรียบเทียบกับคลอรอลไฮเดรตผสมไฮดร็อกซีซีนในการทำให้ผู้ป่วยเด็กสงบ

The sedative efficacy of two combination of midazolam and hydroxyzine compares to chloral hydrate and hydroxyzine in pediatric dental patients

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บทคัดย่อ การศึกษานี้มีวัตถุประสงค์เพื่อเปรียบเทียบความปลอดภัยและประสิทธิภาพการระงับความกังวล ระหว่างการใช้ไมดาโซแลมกับคลอรัลไฮเดรตในผู้ป่วยเด็กที่เข้ามารับการรักษาทางทันตกรรม ออกแบบการศึกษาเป็นแบบสุ่ม สลับกลุ่ม และปกปิดสองทางในผู้ป่วยเด็กอายุ 20-60 เดือน ที่มีสุขภาพแข็งแรงจำนวน 50 คน ผู้ป่วยแต่ละรายอาจได้รับยาไมดาโซแลม (0.5 มก./กก.) ผสมกับไฮดร็อกซีซีน (25 มก.) หรือยาคลอรัลไฮเดรต (50 มก./กก.) ผสมกับไฮดร็อกซีซีน (25 มก.) ในการรักษาครั้งแรก และมีการสลับกลุ่มให้ยาอีกชนิดในการรักษาครั้งที่สอง วัดอัตราการเต้นชีพจร การหายใจ ความอิ่มตัวของออกซิเจน ประเมินความทรงจำและความวิตกกังวลในแต่ละช่วงเวลา ผลการศึกษาพบว่าไม่มีความแตกต่างระหว่างกลุ่ม ทั้งในแง่สัญญาณชีพ ความทรงจำ และความวิตกกังวล แต่กลุ่มไมดาโซแลมมีข้อดีในแง่ความง่ายของการบริหารยาและผลข้างเคียง เช่น อาการคลื่นไส้ อาเจียน การร้องไห้ ที่น้อยกว่าคลอรัลไฮเดรต ซึ่งถือเป็นข้อได้เปรียบของไมดาโซแลม

คำสำคัญ: ไมดาโซแลม, คลอรอลไฮเดรต, ภาวะการเสียความจำไปข้างหน้า, การคลายความกังวล

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Abstract The objective of the study was to compare the safety and sedating efficacy between midazolam and chloral hydrate in pediatric patients receiving dental treatments. The randomized, crossover, and double-blinded study was performed in 50 healthy patients, age between 20 to 60 months. The subjects received equal volume of either midazolam (0.5 mg/kg) with hydroxyzine (25 mg) or chloral hydrate (50 mg/kg) with hydroxyzine (25 mg) in first visit and alternative drug in second visit. The pulse rate, respiratory rate and oxygen saturation were monitored. Anterograde memory and anxiety were evaluated at specific time points. For the results, there were no differences of physiological signs, amnesia as well as anxiety between two groups. However, midazolam had better compliance, and less side effects such as nausea, vomiting and crying which was the advantages over chloral hydrate.

Key words: Midazolam, chloral hydrate, anterograde amnesia, anxiety.

INTRODUCTION

Although chloral hydrate is frequently used because of its safety and efficacy [1-5], the long-standing action and constant sedative effect are unpredictable[3]. Moreover, its anxiolytic effectiveness in pediatric dental patients is still unclear [6,7] It can induce bradycardia, apnea, and can decrease oxygen saturation. The cardiovascular effect of chloral hydrate is significant comparing to other agents, such as oral midazolam[8,9], whereas the duration of action is variable[10]. With less cardiovascular effect[8], midazolam properties includes the anxiolytic, hypnotic, anticonvulsive, muscle relaxant and amnestic[9]. Midazolam has been used for conscious sedation in dentistry with limited support documentation about the efficacy[11-13].

Both chloral hydrate and midazolam have been used in conjunction with hydroxyzine. This antihistamine has sedative and anti-emetic properties. In the recommended dose (25-50 mg), there is no respiratory depression with no-known side effect. Although few studies have compared chloral hydrate and midazolam in terms of patient cooperation[14,15] and anxiety[16-18], there was no investigation of effects on memory function, especially in pediatric patients receiving dental treatment. The objective of the study was to compare the combination of oral midazolam and hydroxyzine with the combination of chloral hydrate and hydroxyzine in the anterograde amnesia, anti-anxiety, onset of action, complication, and compliance aspects.

METHODS

This study was approved by the ethics committee of the Faculty of Dentistry, Prince of Songkla University (PSU), Thailand. The pediatric dental patients who came to the Pediatric Dental Clinic, PSU Dental Hospital were included in this study. The inclusion criteria were as follows, 1) age between 20-60 months, 2) Class I anesthetic risk (the American Society of Anesthesiologists), 3) unable to cooperative ("definitely negative" in Frankl's Behavior Rating Scale[19], 4) require a minimum of restorative treatment and 5) have informed consent from the guardian. The patients were randomly allocated using the coin flipping to get either oral chloral hydrate (50 mg/kg, not exceeding 1 gm) combined with 25 mg hydroxyzine (Group A) or oral midazolam (0.5 mg/kg) combined with 25 mg hydroxyzine (Group B) at first visit. Then they got the alternative drug regimen as crossover design. The schedule timing, examiner, operator, and dental assistant were similar at both visits. The anesthesiologist allocated the patient to drug regimen and dispensation. The patient's guardians got information of the study and signed the informed consent before sedation and operation. The NPO time was at least six-hour.

At the beginning of the visit, the anesthesiologist recorded initial vital signs as well as the oxygen saturation, then continued recording until the patient met the discharge criteria (capability to maintain airway, accomplishing the baseline cardiorespiratory function, normal hydration, and capability to sit up unaided, at least 10 seconds). Critical complications, including respiratory decline, less than 90% oxygen saturation, and more than 25% decrease in mean arterial pressure, were observed.

For the anxiety assessment, an Anxiety Score System modified from Wilton[20] (Table 1) was used to assess the patient. The score was recoded at the following steps, oximeter probe placement, before transferring to treatment room, after papoose board placement and after treatment. Then the freshly prepared cherry distinguished liquid containing either chloral hydrate + hydroxyzine or midazolam + hydroxyzine was given, in body weight corresponding volume according to the assigned group. Each child stayed with guardian in the quiet room until the sign of drowsy was detected, then was transported to the treatment room. The examiner and operator were blind to the sedation regimen.

Table 1 Anxiety Scoring System

Criterion	Score
Agitated: clinging to the parent and/or crying	1
Alert: awake but not clinging to the parent; may whimper but not cry, anxious	2
Calm: sitting or lying with eyes open; relaxed	3
Drowsy: Eyes open, dull reaction. Responds to minor stimulus	3.5
Very drowsy: Eyes closed, dull reaction. Responds to minor stimulus	4
Asleep: Sleeping, no response to minor stimulus	5

For memory assessment, each child was asked to select a picture from the Stanford-Binet Intelligence Scale-Memory for Objects Subjects Subtest [21]. One hour after finishing treatment, the test was repeated.

Data Analysis

Demographic data were presented with descriptive statistics. The differences of physiological effects (vital signs and oxygen saturation) in group A and B were assessed using paired t-test at 95% level of significance. The difference in group A and B patient's anxiety were determined using Wilcoxon matched-pairs signed-ranks test. The non-parametric McNemar matched pairs analysis test was done for nominal-scale memory test.

RESULTS

Fifty patients (24 girls and 26 boys) were recruited in this research. Mean age was 36 months as showed in Table 2. Both regimens were well tolerated as showed in Fig. 1. Midazolam group showed better drug compliance and less nausea and vomiting. The respiratory rates, heart rate, blood pressure and oxygen saturation of both groups were not different. The Fig. 2 and 3 revealed heart rates from the beginning until the termination of treatment with no difference between two groups. For the assessment of anxiety, the scores at different time including anxiety on arrival, applying pulse oximeter, anxiety before treatment, applying papoose board, and anxiety after treatment were showed (Table 3). The Wilcoxon matched-pairs signed-ranks test demonstrated no difference between two groups. The assessment of memory could not be demonstrated in every patient, Fifteen out of 50 failed to recall the picture (33.3% in midazolam group and 66.7% in chloral hydrate group), whereas 18 out of 50 succeed to recall (44.4% in midazolam group and 55.6% in chloral hydrate group). The non-parametric McNemar matched pairs test revealed no difference between two groups (Table 3).

Table 2 Characteristics of the groups

	Total	Drugs	
		Chloralhydrate	Midazolam
Mean Age (months)	50	36.2 ± 8.02	36.4 ± 7.83
Sex	50	25 (50.0%)	25 (50.0%)
Female	24	12 (50.0%)	12 (50.0%)
Male	26	13 (50.0%)	13 (50.0%)
Visit	50		
1st Visit	25	13 (52.0%)	12 (48.0%)
2nd Visit	25	12 (48.0%)	13 (52.0%)

Table 3 Mean anxiety scores in each step and memory test result by drug used

Result	Midazolam	Chloralhydrate	*p*-Value
Anxiety			
- On arrival	2.96 ± 0.046	2.88 ± 0.09	0.414
- Pulse oximeter	2.36 ± 0.20	2.46 ± 0.18	0.258
- Before Treatment	3.46 ± 0.06	3.70 ± 0.20	0.225
- Papoose board application	2.59 ± 0.25	3.31 ± 0.27	0.107
- After treatment	2.94 ± 0.06	2.98 ± 0.05	0.581
Memory test			
- Failed to recall picture	5 (33.3%)	10 (66.7%)	0.515
- Succeeds to recall picture	8 (44.4%)	10 (55.6%)	0.515
- Refused to recall pictures	11 (68.8%)	5 (31.3%)	-
- Questionable	1 (100%)	0 (0%)	-

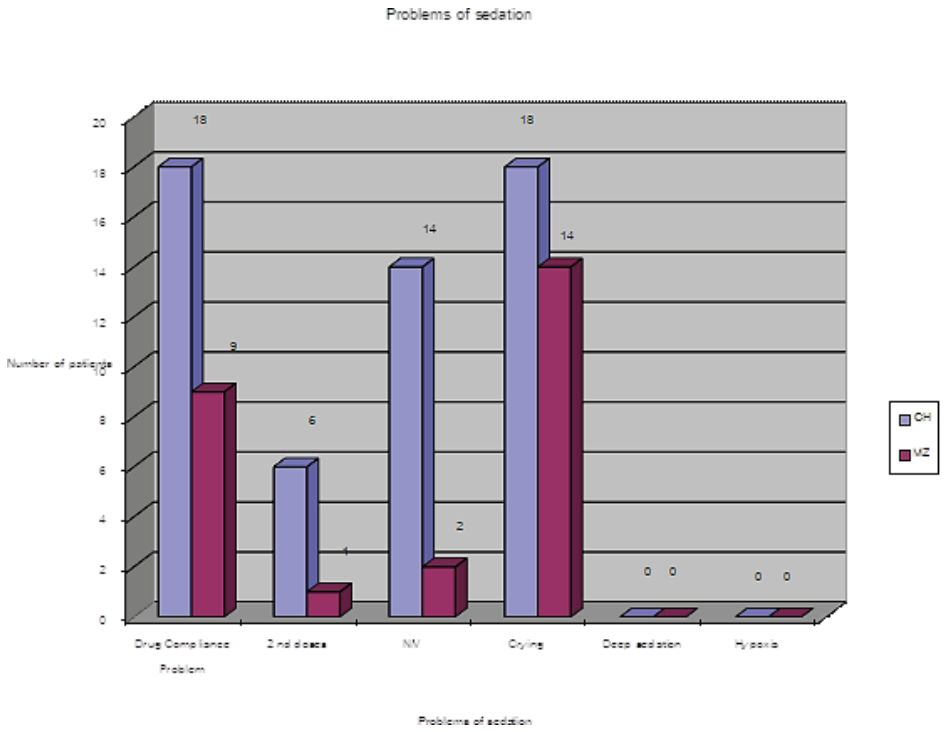

Figure 1 Number of children in each category of problems of sedation

(Drug compliance problem, 2nd dose, N/V (= nausea/vomiting), Crying, Deep sedation, Hypoxia).

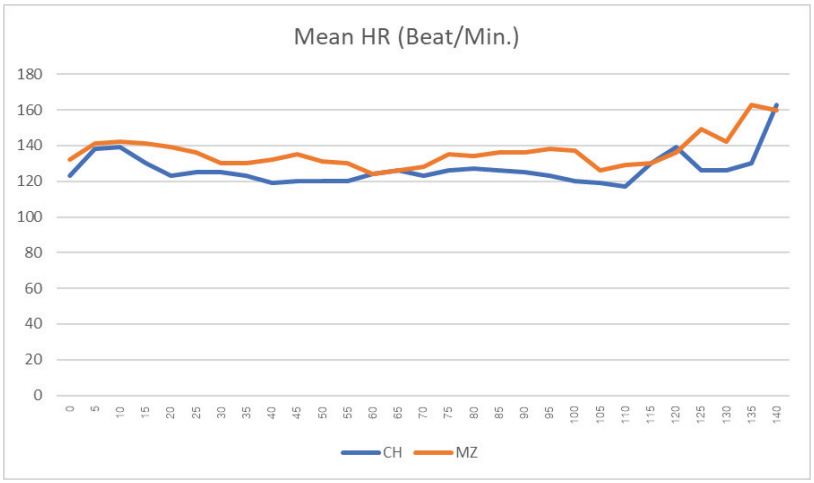

Figure 2 Mean heart rate of subjects compare between chloralhydrate and midazolam.

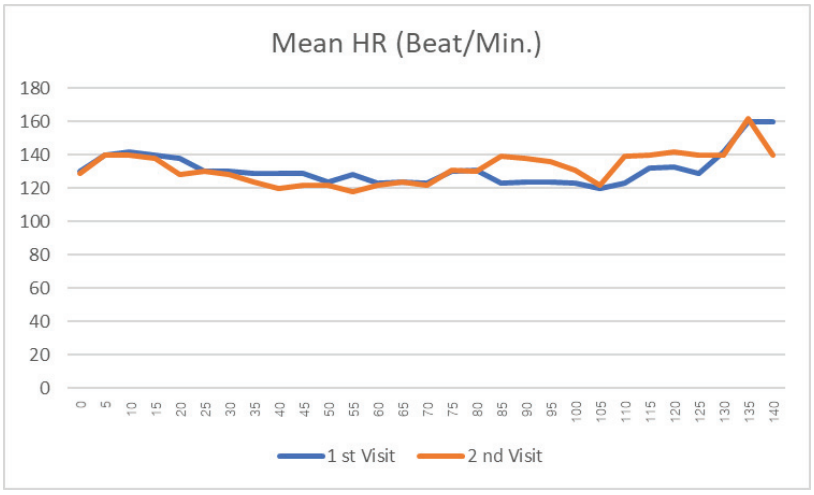

Figure 3 Mean heart rate of subjects during the first and the second visits.

DISCUSSION

Conscious sedation is a preferred choice in pediatric patient. It can reduce the pain distress and worry about treatment, as well as promote co-operation in the next visit. The sedation can be done with various sedative agents and routes, but the oral route is the most preferred route. Midazolam is a safe and effective sedative agent[22,23] with rapid onset[24,25]. In this study, the 0.5 mg/kg dose was selected. This dose was as effective as larger dose for children [26-29]. Field et al reported that the 0.5 mg/kg dose of midazolam was as effective as the 0.75 mg/kg dose in child sedation[30], whereas McMillan et al reported equal effects of 0.5, 0.75 and 1.0 mg/kg doses of oral midazolam in children[31]. Chloral hydrate is sedative-hypnotic agent in non-opioid, non-benzodiazepine group. Because the commercial liquid formulation is unavailable in the market, each hospital prepares its own formulation. The low-dose chloral hydrate (10-25 mg/kg), combined with other sedatives, is used in pediatric dentistry [32]. In this study, chloral hydrate with an anti-emetic, hydroxyzine, was used. A total dose did not exceed 1 gm to avoid the toxicity. The proper level of sedation for management behavior has to be considered in performing extensive procedures in children under 6 years old[33]. In this study, observation was continued throughout post drug-administration time, and the changes in vital signs was within limit. No complication, such as hypoxia or sedation, was detected in both groups. However, in previous articles, unfavorable complications were reported[34,35]. Assessment of memory function is complicated in young children because of variation of child development and imprecise reactions which is not related to recall function[36]. The realizing and recall ability may be affected by increased

apprehension or exhaustion from dental treatment. Recognition tests are less difficult to perform and less sensitive to different developments. Boyd recommended the clinical assessment of memory in children[37], using memory task of recognition, which was used in this study.

CONCLUSION

We performed a clinical trial to compare the efficacy of oral midazolam (0.5 mg/kg) to those of chloral hydrate (50 mg/kg) in less-than five-year pediatric patient receiving dental procedures. The effectiveness in term of anterograde amnesia (effects on memory function) and anti-anxiety was comparable in both medications. However, midazolam had at least 3 advantages; less complication, better drug compliance and shorter onset of action which could reduce a dental visit time.

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