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□ 원 저 □

The Comparison of Behavioral Response of Additional Submucosal Midazolam with Oral Chloral Hydrate, Hydroxyzine and Nitrous Oxide for Pediatric Conscious Sedation

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Abstract

소아 진정 치료 시 Chloral Hydrate와 Hydroxyzine 복용 후 구강 점막으로 투여한 Midazolam의 행동 반응 비교

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배경: 소아 진정 치료 시 서로 다른 용량의 chloral hydrate와 hydroxyzine을 복용 후 midazolam을 구강 점막 하 주사했을 때 행동 반응을 비교하였다.

방법: 총 32회 진정법을 통해 치과치료를 받은 30명의 나이 24-72개월, 체중 20 kg 미만의 미국마취과학회 신체등급 I의 건강하지만 겁이 많고 협조가 안 되는 소아 환자를 대상으로 2개 치아 이상의 보존 치료 및 발치를 필요로 하는 환자를 대상으로 하였다. 호흡기 질환이 있는 아이들은 이 연구에서 제외되었다. 연구 계획은 이대 목동 병원의 임상 실험 심사 위원회에 제출되었다. 1군은 chloral hydrate 50 mg/kg와 hydroxyzine 1 mg/kg 복용 후 점막 하 midazolam 0.2 mg/kg을 추가 투여했고 2군은 chloral hydrate 60 mg/kg와 hydroxyzine 1 mg/kg 복용 후 점막 하 midazolam 0.1 mg/kg을 주사 받았다. 50% nitrous oxide는 치료 중 두 군 모두 유지되었다. 전날 수면 시간과 약물 복용 태도를 기록하였으며 모든 치료 과정은 비디오로 촬영되었다. 맥박 산소 계측기를 이용하여 경피적 산소 포화도와 맥박수를 기록하였고 행동 반응은 Houpt scale을 이용하여 매 2분마다 40분 동안 기록되었다. 전반적인 행동 반응은 Houpt scale를 이용하여 평가되었다. 모든 자료는 SPSS 통계 프로그램을 이용하여 two sample independent t-test를 사용하였다. P 값은 0.05 미만인 경우를 통계학적으로 유의하다고 보았다.

결과: 두 군 간의 경피적 산소 포화도와 맥박수는 모두 정상 범위이며 유의한 차이가 없었다. 행동 반응 비교에서는 치료 처음 10분 동안 2군이 1군에 비해 점수가 높게 나왔으며($P < 0.05$), 그 외에는 유의한 차이가 없었다. 전날 총 수면 시간과 약물을 복용하는 태도는 수면 치료 중의 행동 반응에 영향을 주지 않았다.

결론: Chloral hydrate 50 mg/kg 복용과 점막 하 midazolam 0.2 mg/kg은 chloral hydrate 60 mg/kg 복용과 점막 하 midazolam 0.1 mg/kg과 비교할 때 두 약물의 조합은 모두 소아 환자 수면 치료 시 안전하고 효과적인 용량이다. Overall behavior와 Q (quiet)의 분포를 비교해 볼 때 두 군 모두 성공적인 진정효과를 기대할 수 있다. **(JKDSA 2007; 7: 6~12)**

핵심용어: Conscious sedation, Submucosal midazolam, Chloral hydrate, Hydroxyzine

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INTRODUCTION

Various drug regimens and routes of delivery are introduced to sedate children who are anxious and uncooperative during dental care (Primosch et al, 2001; Wilson et al, 2000; Dallman et al, 2001; Nathan, 1987). Combinations of sedative drugs are essential to pharmacologic management techniques in pediatric dentistry (Needleman et al, 1995; Nathan, 1989). One of the most popular combinations for achieving sedation in children is the use of chloral hydrate, hydroxyzine, and nitrous oxide (Houpt, 1993).

Chloral hydrate (CH) has been one of the most frequently used agent, but the agent has variable absorption, bitter taste and causes gastric irritation (Moore, 1984). Therefore, the effectiveness of CH in achieving desired sedation is highly variable (Nathan, 1989). Previous study using this combinations reports success rates ranging from 18 to 90% (Nathan, 1989). Due to these success rates primarily being dependent upon the dosage of CH, some dentists have tried to raise the success rate just by adding more CH. But, adding more CH leads to more concern about gastric irritation and lengthy postoperative recovery time. Therefore, the tendency has been focused on combination of different sedative agents such as midazolam, a short-acting benzodiazepine, keeping the dosage of CH as 50 mg/kg which is the manufacturer's recommended dose (Nathan, 1989).

Midazolam is a benzodiazepine possessing hypnotic, anticonvulsant, muscle relaxant, antegrade amnestic and anxiolytic activity (Kupietzky et al, 1993). It has a rapid onset and recovery. It also has a reversible agent. Especially, its anterograde amnestic effect might be very important for young and anxious children who need more sedative treatment in near future (Krupietzky et al, 1996).

Recently, a 5-year pilot study by Griffin (Griffin, 2000) introduced that the submucosal (SM) route of midazolam has been great deal of notice as viable technique for drug administration and also an effective route for conscious sedation. Even titration is possible due to the slow absorption from the mucobuccal fold (Griffin, 2000). Another recent study by Myers et al (Myers et al, 2004) showed that SM midazolam combined with oral CH improved the quality of sedation without compromising safety.

The advantage of SM midazolam with oral CH is to minimize oversedating children by keeping lower dosage of oral CH dosage, which decreases nausea, vomiting and postoperative recovery time. Furthermore, midazolam has a reversal agent, flumazenil, which increases the safety of the sedation (Davies et al, 1990).

The purpose of this study was to compare the behavioral response and assess the effectiveness of two different dosages of submucosal midazolam and oral CH when used for pediatric conscious sedation in dental procedure. The clinical hypothesis for this study was that there would be no difference in behavior between two groups.

METHODS

This protocol was submitted to the Human Subjects Institutional Review Board (IRB) of Ewha Womans University Hospital. Thirty two uncooperative, young children between the ages of 24 and 72 months old, weight less than 20 kg, healthy (ASA I) patients participated in this study. Patients had more than 2 teeth of restorative need, extractions or sutures. Those were excluded from the study if they had any report of respiratory problems, such as a common cold or influenza.

At the initial appointment each patient was examined by the resident of pediatric dentistry at Ewha womans university hospital to assess behavior. The proposed treatment plan was explained to the parents and informed consent was obtained.

On the day of sedation, medical history and nothing by mouth (NPO) status were reviewed with the parent. Preoperative oxygen saturation and pulse rate were obtained using pulse oximeter (Nellcor co, Plea-

Table 1. Rating Scale for Sedation by Houpt

	Score	Crying	Movement
Q (Quiet)	4	No crying	No movement
M (Movement)	3	No crying	Controllable, not interfering with treatment
C (Crying)	2	Controllable, not interfering with treatment	No movement
S (Struggling)	1	Continuous, hysterical	Violent, interrupting

sant, USA). Total amount of hours that the patient slept the night before operation was also recorded. Patients were randomly assigned into one of two groups: group 1 received oral CH (Pocral®, Hanlim Pharm. co. Korea) 50 mg/kg and hydroxyzine (Ucerax®, Hanmlim Pharm. co. Korea) 1 mg/kg. group 2 received oral CH 60 mg/kg and hydroxyzine 1 mg/kg. The acceptance of oral medications was evaluated using a three point scale where 3 is good (cooperative, unafraid), 2 is moderate (slightly fearful, hesitate to taking), 1 is poor (crying, forcefully taking).

After 45 minutes, the patients were separated from the parents and carried to the treatment room where pulse oximeter was affixed on the left first toe. The patient was secured on a papoose board. A nasal mask was placed over the child's nose and 50% N_2O was delivered. A videotape recording of each appointment was started as the child was brought into the room. Topical and local anesthetics were delivered and midazolam (Dormicum®, Bukwang Pharm. co. Korea), group 1: 0.2 mg/kg, group 2: 0.1 mg/kg, was administrated on maxillary non-working side of buccal vestibule submucosally. Once the patient was fully sedated, the nasal hood was replaced with the nasal mask. Treatment was started and pulse rate and percutaneous oxygen saturation were recorded every 2 minutes. The behavior responses were rated using a rating scale described by Houpt (Table 1) (Houpt et al, 1989).

The scores were recorded every 2 minutes for 40 minutes. A child's overall behavior at the completion of the procedure was recorded similar to Houpt's scale of overall behavior (Table 2) (Houpt et al, 1989). Patient's behavior was considered effective when the scores ranged from 5 to 6 and ineffective when it was scored 1 to 4.

Table 2. Rating Scale for Overall Behavior by Houpt

Score	
6	Excellent - no crying or movement
5	Very good - some limited crying or movement
4	Good - difficult but all treatment performed
3	Fair - treatment interrupted but eventually all completed
2	Poor - treatment interrupted, only partial treatment completed
1	Aborted - no treatment rendered

The results were analyzed using two sample independent t-test by SPSS (version 11.0.1, SPSS Inc, USA) statistics program. The statistical difference was judged significant at the $P < 0.05$.

RESULTS

Physiologic and behavioral data were collected from 32 sedations involving 21 males and 11 females, who ranged in age from 24 to 60 months old. The weights of patients ranged from 10.5 kg to 20.0 kg. There were no significant differences between the two groups with respect to age, weight, gender, total amount of sleep the night before procedure and the acceptance of medication (Table 3).

An independent t-test was used to determine significance in physiologic parameters between the two groups. There were no significant differences between two groups for percutaneous oxygen saturation (SpO_2) and pulse rate (PR) (Table 4). In the total of 32 sedations for these patients, there were 3 reports of desaturation incidents, which SpO_2 level went down

Table 3. Demographic Data

	Group 1	Group 2	P value
Age (months)	42.1 ± 10.4	34.7 ± 10.3	0.05
Weight (kg)	16.0 ± 2.4	15.2 ± 2.4	0.37
Gender (Male/Female)	10/6 (16)	11/5 (16)	0.30

The values are mean ± SD

Table 4. Percutaneous Oxygen Saturation and Pulse Rate

	Group 1	Group 2	P value
SpO_2 (%)	98.8 ± 0.8	98.9 ± 0.8	0.78
PR (/mm)	98.7 ± 0.8	98.9 ± 0.8	0.62

The values are mean ± SD
SpO_2: percutaneous oxygen saturation
PR: pulse rate

Table 5. Stepwise Behavior Scores throughout Treatment Procedure

	Group 1	Group 2	P value
<10 min	3.5 ± 0.6	3.9 ± 0.3	0.01
10 to 20 min	3.9 ± 0.2	3.9 ± 0.3	0.90
20 to 30 min	3.8 ± 0.5	3.8 ± 0.5	0.73
30 to 40 min	3.5 ± 0.3	3.8 ± 0.4	0.84
0 to 40 min	3.7 ± 0.2	3.8 ± 0.3	0.32

The values are mean ± SD

below 95 but quickly went up by head positioning of triple airway maneuver and mouth suctioning. The pulse rate increased during injections, insertion of mouth prop, or placement of rubber dam, but quickly decreased to normal when the stimuli disappeared.

The four scores of the Houpt sedation rating scale (Quiet, Movement, Crying, and Struggling) were used to compare the efficacy of the two groups. An independent t-test was utilized to determine significance in mean score of the behavior response during treatment. The only behavior score showing a statistically significant difference ($P < 0.05$) between two groups was mean score for the first ten minutes. Group 2 showed the better behaviors during the first ten minutes (Table 5). No other significant differences were found in behavior between the two groups during the rest of period.

Neither the total amount of sleep the night before operation nor the acceptance of medication appeared to have significant effects on the behavioral response during the sedation period (Table 6).

The effectiveness of the sedation was also determined by analyzing the percentage of the overall behavior scores and Q behavior observations in each group (Table 7). The success of sedation included ratings of 5 and 6 in overall behavior and the higher percentage of Q behavior. No significant differences were observed between the two drug doses regarding overall behaviors and Q behavior.

Table 6. Total Amount of Sleep Hours and Acceptance of Medication

	Group 1	Group 2	P value
Total amount of sleep (hours)	8.5 ± 1.0	8.6 ± 1.9	0.97
Acceptance of medication	2.6 ± 0.7	2.4 ± 0.7	0.47

The values are mean ± SD

Table 7. Overall Behavior and Q Behavior Percentage

	Group 1	Group 2
Overall behavior scores (5 or 6) (%)	81.3	87.5
Q behavior (%)	83.8	90.6

DISCUSSION

Several drug combinations have been used for sedation in pediatric dentistry. The most popular one is CH, hydroxyzine, midazolam and frequently supplemented with nitrous oxide/oxygen (Fuks et al, 1994). Oral CH has variable absorption, causes gastric irritation and vomiting (Dallman et al, 2001). Hydroxyzine is used safely as a sedative agent for many years. It is an antihistamine with sedative and antiemetic properties. There is no respiratory depression (Shapira et al, 2004). Midazolam has rapid onset, short duration of action, anterograde amnestic properties (Dallman et al, 2001). From based on all these advantages and disadvantages of above drugs, CH and hydroxyzine combined with midazolam have many possible positive interactions that should be investigated.

This study shows that the combination of oral CH and SM midazolam with hydroxyzine supplemented by 50% nitrous oxide/oxygen inhalation is a safe and effective approach to sedate young children for dental treatment. Recently, a study has been published investigating the effectiveness of SM midazolam combined with oral CH (Lee et al, 2005). SM midazolam improved the quality of sedation and vomiting response. The children sedated with additional SM midazolam were more likely to exhibit quiet and sleep behavior than oral CH and hydroxyzine alone. Another study using BIS index during sedation procedure showed that SM midazolam improved the sedation quality by deepening sedation depth without compromising safety and enabled the sadation pattern to stay more stable (Lee, 1996). This study confirmed that adding SM midazolam seems to be safe with no adverse effects on vital signs at both dosages and effective in the sense that its duration of action permits sufficient time to successfully complete routine operative dentistry during sedation.

The 50 mg/kg of oral CH, the manufacturer's recommended dose, often leads to undersedate the children and abort treatment in the end. When this happens, by adding SM midazolam in the middle of treatment, the sedation can be completed safely and successfully. It has been known that the oral CH 50 mg/kg and SM midazolam 0.2 mg/kg is safe and effective combination for sedating young children in the dental treatment without oversedating patients by initially given increased dosage of oral CH (Myers et al, 2004). Therefore, the choice of the dosage of 0.2 mg/kg of SM midazolam in group 1 was based on a previous study in which 0.2 mg/kg of SM midazolam and 50 mg/kg of oral CH had been used (Myers et al, 2004). For the safety reason, SM midazolam was decreased to 0.1 mg/kg as oral CH was increased to 60 mg/kg in group 2. Also, the United States Pharmacopeial Dispensing Information recommended 0.1−0.15 mg/kg IM dosage for children (Thomas MICROMEDEX, 2005). The SM route is a similar parenteral method of administration to IM route and they have shown similar absorption and elimination of midazolam (Alfonzo-Echeverri et al, 1990).

This study results showed that there was a statistically significant difference ($P < 0.05$) between two groups in mean behavior scores during the first ten minutes. The possible explanation of this result was that the higher dosage of CH had influenced on the quieter behavior in group 2 during the first ten minutes of sedation. Another explanation was that while there was no significant difference for behavior ratings between two groups, the children in group 2 were younger than those children in group 1 (34.7 months old vs. 42.1 months old, respectively). It is possible that the sedation during the first 10 minutes had related-effect to age and weight, favoring cooperative behavior in younger and less weighted children. Further studies may be needed to examine this hypothesis. No other significant differences were found in behavior between the two groups during the rest of period.

The most grateful property of midazolam is its antegrade amnestic effect. Although this study didn't make great effort to check the amnestic effect of midazolam, it was assumed that the child couldn't recall of the injections or the operative procedure itself, which would positively influence on following appointment.

The results of the present study did not support the hypothesis that total amount of sleep the night before procedure and the compliance to oral drug administration correlated with behavior during dental treatment. There were no statistically significant differences between the intraoperative behavior scores regardless of how many hours a child sleeps the night before or whether the medication was accepted willingly or forced. Therefore, both parameters mentioned above were poor predictive values in determining the overall quality of the sedation procedure.

The results showed the overall effectiveness of the combination of agents used in this study in reducing anxiety and improving child behavior. By Myers et al (Myers et al, 2004), mean percentage of Q behavior in CH and midazolam regimen was 84%, which showed the similar result to that of this study (83.8%). The score 4 in the overall behavior ratings wasn't considered as the effective sedation score in this study. If the score 4 was included as one of effective sedations, the percentage of overall effectiveness would be increased much higher. Therefore, two drug dosages used in this study were both effective in order to perform the operative dental treatment successfully across 40 minutes sedation period.

Results of this study had limitations which include multiple operators, who do not blinded to the dosage of drugs.

More research is needed to determine the recovery time after different dose of sedation, and dosage combination which is the most effective for the pediatric sedation. Further investigation is needed to examine that patient's character or weight may play an important role in sedation quality.

CONCLUSION

1. The SM midazolam 0.2 mg/kg and oral CH 50 mg/kg is as safe and effective as the SM midazolam 0.1 mg/kg and oral CH 60 mg/kg for sedating young children in dental treatment.
2. Mean SpO_2 and pulse rate were maintained within the normal range for both groups.
3. The quality of sedation is successful and satisfied in both groups.
4. The total amount of sleep the night before treatment and acceptance of oral sedative agents were poor predictive values in determining the overall quality of the sedation procedure.

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