Effect of midazolam and hydroxyzine compares to chloral hydrate and hydroxyzine in sedating pediatric dental patients

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Abstract

This prospective, randomized, and double-blind study compared the safety and effectiveness of a mixture of midazolam and hydroxyzine to that of chloral hydrate and hydroxyzine in sedating pediatric dental outpatients Twenty-five healthy children aged 20 to 60 months who exhibited "negative" behavior during a screening visit were included in the study. All required at least two visits for restorative treatment with each subject serving as his/her own control. They received, by mouth, identically appearing liquids of equal volume of either midazolam (0.5 mg/kg) with hydroxyzine (25 mg) or chloral hydrate (50 mg/kg) with hydroxyzine (25 mg) for the first visit and the alternative regimen for the second visit. Pulse rate, respiratory rate and blood oxygen saturation levels were monitored before, during and after the operative procedures. Anxiety and the child's anterograde memory were assessed at specific time points. All the treatment sessions were video recorded and evaluated independently by three pediatric dentists during specific procedures (injection, mouth gag and rubber dam placement) and at specific time intervals (5, 10, 15, 30, 45, 60 minutes). The data were entered into SPSS for analysis. No statistically significant differences between the two pharmacological regimens with regard to crying, the degree of anterograde amnesia, effects on memory function, physiological effects, and antianxiety effect. However, midazolam was better than chloralhydrate in controlling overall behavior and drug compliance of children undergoing dental procedures as outpatients. (This study was supported by Prince of Songkla University, Hadyai, Songkla, Thailand.)

Introduction

Although most of pediatric dental patients can be treated using traditional behavior modification, some fearful and unco-operative patients need pharmacological sedation to overcome their behavior. Consequently, effective dental treatments can be carried out successfully. Among those drugs used for oral sedation, chloral hydrate is often used because of its wide margin of safety [1,2].

Chloral hydrate is a time-honored sedative-hypnotic, widely used for pediatric sedation. Although its safety and efficacy are well documented [3, 4, 5], concerns remain about its prolonged duration of action and the consistency of sedative effects [3]. In addition, the efficacy of chloral hydrate as an anxiolytic agent has been questioned frequently. There are a few animal studies of the sedative and antianxiety effects of chloral hydrate [6,7], but clinical use and research have not clearly established the anxiolytic effectiveness in pediatric dental patients.

Oral midazolam has been used for sedation with few cardiovascular effects [8]. Midazolam has been claimed to have the anxiolytic, hypnotic, anticonvulsant, muscle relaxant and amnesic properties [9]. It is relatively free of side effects when used alone and offers several advantages over traditional pharmacological agents such as chloral hydrate [10]. It is being used for conscious sedation in dentistry with little documentation assessing its efficacy [11, 12, 13].

Hydroxyzine is an antihistamine with sedative and anti-emetic properties. It has been used in conjunction with chloral hydrate or midazolam to reduce the incidence of nausea and vomiting and to increase the sedative effect. There is no respiratory

depression and no known side-effects when used in the recommended doses (25-50 mg.) [14].

Although few studies have compared the use of chloral hydrate and midazolam for patient cooperation [15, 16] and anxiety [17,18, 19], none have closely investigated their effects on memory function in pediatric dental patients.

The purposes of this study are to evaluate in a randomized, double-blinded fashion the safety and effectiveness of oral midazolam and hydroxyzine compares to chloral hydrate and hydroxyzine for the degree of anterograde amnesia, effects on memory function, physiological effects, antianxiety effect, sedative effect and behavioral responses of children undergoing dental procedures as outpatients.

This study has been approved by the ethic committee of the faculty of dentistry, Prince of Songkla University.

Methods

The subjects were pediatric dental patients who seek treatment at a pediatric dental clinic, Price of Songkla University (PSU) dental hospital. The inclusion criteria were as following:

1. The patient's age was between 20-60 months.
2. The patient's anaesthetic risk category was classing I according to the classification of the American Society of Anesthesiologists. (Class I: no organic, physiologic, biochemical or psychiatric disturbance)
3. The patient was unco-operative ("definitely negative" in Frankl's behavior rating scale [20]) at the time of examination.

4. The patient required a minimum of two visits for restorative treatment.
5. Informed consent for inclusion in the study was obtained.

The subjects were assigned randomly by flipping the coin to receive either oral chloral hydrate 50 mg/kg, not to exceed 1 gm, combined with 25 mg hydroxyzine (group A); or 0.5 mg/kg oral midazolam combined with 25 mg hydroxyzine (group B) for the first visit, and the alternative drug regimen at the second visit. Consequently, a crossover design was used, with each subject serving as his/her own control. The time of the day, examiner, operator, dental assistant was constant at each of the two visits. Assignment of the patients to a drug regimen and administration of the drugs was the responsibility of an anesthesiologist.

Patients' guardians of all subjects completed a consent form and were given preoperative and postoperative instructions before the sedation appointment. An explanation of the study was given and any question was answered. On the day of sedation appointment subjects had nothing to drink or eat 6 hours before the procedure. All appointments were held at 8 am.

Assessment of physiological effects

Up on arrival, patient's initial respiratory rate (RR), heart rate (HR), arterial blood pressure (BP), and pulse oximetry were obtained. Safety measures included continuous monitoring of pulse oximetry and intermittent assessment of RR, HR and BP to evaluate for cardiorespiratory depression until the child met pre-established discharge criteria. These recovery criteria included the ability of the patient to maintain a patent airway, achieve baseline cardiorespiratory function, normal hydration, and the ability to sit up

unaided, when appropriate, for 10 second or longer. Serious complications were defined as respiratory depression required assisted ventilation, oxygen saturation less than 90%, or a 25% or greater decrease in mean arterial blood pressure.

Data analysis

Paired-t test was used to test the significance of differences in physiological effects to patients receiving either chloral hydrate with hydroxyzine or midazolam with hydroxyzine. The test was used at 95% level of significant. Descriptive statistic was used for demographic data.

Assessment of anxiety

On arrival, each child was assessed by the examiner using an anxiety scoring system (Table 1) modified from Wilton [21]. The scores were also recorded at the following steps including oximeter probe placement, before carrying to the treatment room, after wearing a papoose board, and after treatment.

The child was then offered freshly prepared by an anesthesiologist, identically appearing, cherry flavored liquids in body weight equivalent volumes. The liquid contained either choral hydrate and hydroxyzine or midazolam and hydroxyzine. These liquids were administered to each child depending on which regimen is randomized selected for the child at that visit. Group A was administered chloral hydrate plus hydroxyzine in cherry flavored liquid. Group B was administered midazolam plus hydroxyzine in cherry flavored liquid. The examiners, operators and investigators were 'blind' to the treatment regimen. Following drug administration, each child remained

with the parent in the quiet room until the sign of drowsy was detected. The child was then carried into the treatment room.

Data analysis

Since all data were ordinal with related samples, non-parametric statistic was used. The Wilcoxon matched-pairs signed-ranks test was used to test the significance of differences in anxiety of patients receiving either chloral hydrate with hydroxyzine or midazolam with hydroxyzine. A P value of ≤ 0.05 was accepted as being significant.

Assessment of memory

Apart from anxiety assessment, the child's anterograde memory was also assessed using the following protocol. Before entering the treatment room, each child was asked to select a picture from the Stanford-Binet Intelligence Scale – Memory for Objects subjects subtest [22]. The child picked up a picture from a large array of pictures consist of common objects (e.g., shoe, car, banana, etc.). Parent (s) was presented but was asked to refrain from commenting or assisting the child. This procedure was repeated again 1 hour after termination of treatment and transferring the child to the quiet room. During the alternative session, different set of the pictures were randomly shown so that each subject was shown a set of pictures not previously shown.

Data analysis

Since the rating scales used the nominal scale of measurement with related samples, the non-parametric McNemar matched pairs analysis test was used at the 95%

level of significance. The treatment group was designed so that each subject served as its own control in a crossover design. The independent variable was the type of drug administered and the dependent variable was its effect on the child memory.

Assessment of behavior

After entering the treatment room, the child was restrained in a Papoose Board, which was used for all patients, even though well sedated, for their safety. Vital signs were monitored continuously with a finger pulse oximeter (Model 3700e, USA) and stethoscope.

The dental procedures were videotape from the time the child was admitted to the treatment room until the treatment was completed and the child left the dental chair. Three pediatric dentists who were 'blind' to the drug given, independently evaluated each patient's behavior (degree of crying, movement and sleep, and overall behavior) during specific procedure, namely local anesthetic administration, mouth prop insertion, rubber dam placement, and at 15-minute intervals during treatment. The rating scale used (Table 2) was developed by Nazif [23] and Houpt *et al.* [24], and had the utility in evaluating quantitative as well as qualitative aspects of pharmaco sedation [25]. It was operationally defined in term of the effect of behavior on the progress of treatment [26], and the worst occurring behavior was rated each time. The evaluators did not discuss the recording or their decisions and, in the case of disagreement in ratings, the majority rating was accepted.

Data analysis

Since all data were ordinal with related samples, non-parametric statistic was used. The Wilcoxon matched-pairs signed-ranks test was used to test the significance of differences in behavior of patients receiving either chloral hydrate with hydroxyzine or midazolam with hydroxyzine. The Mann-Whitney U test was used to test the significance of different in behavior related to the order of drug administration and the sex of the patients. For both tests, a P value of ≤ 0.05 was accepted as being significant.

Results

Table 3 shows characteristics of the groups

The various parameters under consideration were observed, recorded and results were summarized as follows:

Assessment of physiological effects

Both regimens were well tolerated by the patients without any serious problems as shown in figure 1. Midazolam gave significant better results than chloral hydrate in terms of drug compliace and side effect of nausea and vomiting. There was no significant difference between the two pharmacological regimens with regard to respiratory rate (RR), heart rate (HR), arterial blood pressure (BP), and pulse oximetry Figure 2 and figure 3 show heart rate of subjects recorded starting from the beginning of treatment until the treatment procedure was done. No significant difference was detected between the two pharmacological regimens, no matter what visit they were used.

Assessment of anxiety

Table 4 shows mean anxiety score by drug used at different time period including on arrival, pulse oximeter application, before treatment, papoose board application, and after treatment. No statistically significant difference (Wilcoxon matched-pairs signed-ranks test) was found between the two pharmacological regimens with regard to anxiety scores.

Assessment of memory

Although the possible total numbers of the tests was 50, this did not always.happen because it was not possible for it to be carried out. Table 5 and 6 show the results of memory tests. Children who refused to recall picture did that 16 out of 50 visits. About 69% of them were under midazolam sedation where as 31% were under chloralhydrate sedation. Chidren who failed to recall picture did that 15 out of 50 visits. About 33% of them were under midazolam sedation where as 67% were under chloralhydrate sedation. Chidren who succeed to recall picture did that 18 out of 50 visits. About 44% of them were under midazolam sedation where as 56% were under chloralhydrate sedation.

No statistically significant difference (non-parametric McNemar matched pairs) was detected between the two pharmacological regimens with regard to children memory.

Assessment of behavior

The results of behavior assessment are presented in table 7, 8 and 9. Table 7 shows the number of children in each crying rating during dental procedure under sedation with chloralhydrate compare to midazolam. Those of movement and overall behavior ratings are demonstrated in tale 8 and table 9 respectively.

No statistically significant difference in the two pharmacological regimens was detected with regard to crying (Table 7).

Table 8 indicates the rating of movement at the same time that crying was evaluated. The only significant difference was at 45 minites when chloralhydrate demonstrated better control of movement than midazolam. The differecet was not significant for the rest of the time.

Interestingly, midazolam exhibits better results in term of overall behavior. As can be seen from table 9, almost all rating time (7 out of 9 steps) midazolam control overall behavior significantly better than chloralhydrate. No significant difference was detected at the time of injecting local anesthesia and at 30 minutes.

Using Mann-Whitney U test, no significant difference in behavior was found related to either the order of administration of the drugs or the gender of the patients.

Discussion

In pediatric dentistry, the state of conscious sedation may be desired in a number of cases, especially in small children because it reduces the fear of pain and anxiety associated with dental procedures and makes patient co-operative for future dental appointments. The state of conscious sedation can be achieved through variety of

pharmacological agents administered through various routes, but oral route is usually the most preferred one for pediatric dental patients.

Midazolam was chosen in this study because its sedative effects in patients undergoing surgical procedures. A few workers have already worked on oral midazolam as an agent to produce conscious sedation. They found it safe and effective [27, 28] with rapid onset of sedation [29, 30]. But still there is not much literature available on the oral use of midazolam. The 0.5 mg/kg dose was selected secondary to being equally effective to larger doses in children [31-34] Field *et al* demonstrated that 0.5 mg/kg was equally effective as 0.75 mg/kg in the sedation of pediatric patients [35]. McMillan *et al* demonstrated that sedation and anxiolysis did not differ among children who received 0.5, 0.75, 1.0 mg/kg of oral midazolam [36]. Peak sedative effects of midazolam occur at 30 minutes after oral administration [33].

Chloral hydrate 50 mg/kg with hydroxyzine 25 mg was chosen to its being a common regimen in the pediatric dental literature. Hydroxyzine was added to chloral hydrate to potentiate the effect of the relative low dose of the latter, and as an anti-emetic agent. A total dose not to exceed 1 gm was chosen in an attempt to avoid toxicity. Nitrous oxide supplementation was not used secondary to the desire of the authors to eliminate any synergistic drug effects from the study and adverse long term effects to dental personale.

A close observation on all patients was kept throughout the post drug administration period, because adverse reactions were reported by many investigators [37, 38]. However, in present study the alteration in pulse rate, heart rate, blood pressure

and respiratory rate were within physiological limits and no serious adverse reactions such as hypoxia or deep sedation were observed in any patient in both regimens.

Memory is difficult to evaluate in young children because they frequently make inaccurate responses independent of memory function and because developmental influences vary with age [39]. Increased anxiety or fatique (due to dental treatment) may interfere with learning and the ability to recall. Recognition tasks are less difficult to perform and are less sensitive to developmental differences. In this study the anterograde memory loss (the inability to recall from the period subsequent to drug administration) in children was, therefore, evaluated utilizing the memory task of recognition, a recommended mode of sampling memory phenomenon in children [40].

From the results of the present study, it can be stated that comparing to chloralhydrate, oral midazolam at the dose used in the study reliably and rapidly produces an appropriate degree of sedation in child patients undergoing dental procedures as outpatients in term of the degree of anterograde amnesia, effects on memory function, physiological effects, antianxiety effect, sedative effect and behavioral responses. Moreover, midalzolam should be considered as a better drug of choice than chloralhydrate, "a time-honored sedative-hypnotic", for the following reasons. Firstly, midazolam created less drug compliace problems. Secondly shorter onset.of midazolam reduce a dental visit time for each child. Last, but not least, midazolam produced less sedative complication.

Conclusion

In conclusion, oral midazolam in a dose of 0.5 mg/kg of body weight plus 25 mg of hydroxyzine was as effective as chloral hydrate 50 mg/kg plus 25 mg of hydroxyzine in the sedation of pedodontic patients in term of the degree of anterograde amnesia, effects on memory function, physiological effects, and antianxiety effect. However, midazolam was better than chloralhydrate in controlling overall behavior and drug compliance of children undergoing dental procedures as outpatients.

Acknowledgments

This study was supported by Prince of Songkla University, Hadyai, Songkla, Thailand

The authors thank Mr. Mitchell Allan Bruce Atkins and Ms. Jude Sowden for their critical reading of the manuscript.

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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

Table 2. Behavior rating scales used are as following:

Ratings	Rating code
Crying	
Hysterical crying	1
Continuous persistent crying	2
Intermittent mild crying	3
No crying	4
Movement	
Movement interrupting treatment	1
Movement making treatment difficult	2
Movement that does not interfere with treatment	3
No Movement	4
Sleep	
Fully awake, alert	1
Drowsy, disorientated	2
Asleep, rousable	3
Asleep, not easily rousable	4
Overall behavior	
Very poor – no treatment rendered	1
Poor – treatment interrupted, only partial treatment completed	2
Fair – treatment interrupted but eventually completed	3
Good – difficult but all treatment performed	4
Very good – some limited crying or movement (eg. During administration of LA or mouth gag insertion)	5
Excellent – no crying or movement	6

Table 3 Characteristics of the groups

	Total	Drugs	
		Chloralhydrate	Midazolam
Mean Age (months)	50	36.16± 8.02	36.44±7.83
Sex	50	25 (50%)	25 (50%)
Female	24	12 (50%)	12 (50%)
Male	26	13 (50%)	13 (50%)
Visit	50		
1st Visit	25	13 (52%)	12 (48%)
2nd Visit	25	12 (48%)	13 (52%)

Table 4 Mean anxiety score by drug used

Time	Chlorahydrate		Midazolam		Wilcoxon Signed Rank	
	n	Mean±SD	n	Mean±SD	Z	P-Value
On arrival	25	2.88 ±0.09	25	2.96 ±0.046	.816	.414
Pulse oximeter	24	2.46 ±0.18	22	2.36±0.20	-1.131	.258
Before Treatment	25	3.70±0.20	25	3.46 ±0.06	-1.214	.225
Papoose board application	24	3.31±0.27	22	2.59 ±0.25	-1.612	.107
After treatment	23	2.98±0.05	24	2.94 ±0.06	-.552	.581

Table 5 Number of children in each category of memory test

	No.	**Chloralhydrate**	Midazolam
▪ Subject who refused to recall pictures	16	5 (31.3%)	11 (68.8%)
▪ Subject who failed to recall picture	15	10 (66.7%)	5 (33.3%)
▪ Subject who succeed to recall picture	18	10 (55.6%)	8 (44.4%)
▪ Questionable	1	0 (0%)	1 (100%)

Table 8 **Number of children in each movement rating during dental procedures under sedation with Chloralhydrate (C) or Midazolam (M)**

Procedure/ Time interval	Drug	Total number	Movement rating				Z	P-Value
			Interrupting treatment	Making treatment difficult	No interfering with treatment	No movement		
Local Anesthesia	C	19	1	8	7	3	-0.81	0.42
	M	19	1	6	7	5		
Mouth prop	C	17	0	3	4	10	-0.30	0.76
	M	19	0	3	6	10		
Rubber dam	C	19	1	10	3	5	-0.27	0.79
	M	19	1	8	6	4		
5 min.	C	19	0	6	2	11	-1.26	0.21
	M	19	0	8	4	7		
10 min.	C	19	0	3	4	12	-1.63	0.10
	M	18	1	4	8	5		
15 min.	C	19	0	3	2	14	-0.75	0.45
	M	17	0	5	8	4		
30 min.	C	18	0	0	6	12	-0.33	0.74
	M	17	0	1	4	12		
45 min.	C	17	0	0	1	16	-2.04	0.04*
	M	14	1	3	2	8		
60 min.	C	12	0	2	1	9	-1.00	0.32
	M	11	0	2	3	6		

Table 9 **Number of children in each Overall behavior rating during dental procedures under sedation with Chloralhydrate (C) or Midazplam (M)**

Procedure/ Time interval	Drug	Total number	Overall behavior rating						Z	P-Value
			Very Poor	Poor	Fair	Good	Very good	Excellent		
Local Anesthesia	C	19	0	0	1	8	8	2	-0.54	0.59
	M	19	0	0	1	8	5	5		
Mouth prop	C	17	0	0	0	3	5	9	-3.53	<0.001
	M	19	0	0	0	4	6	9		*
Rubber dam	C	19	0	0	1	9	5	4	-3.69	<0.001
	M	19	0	0	2	7	6	4		*
5 min.	C	19	0	0	1	6	1	11	-3.53	<0.001
	M	19	0	0	0	8	4	7		*
10 min.	C	19	0	0	0	4	3	12	-3.35	0.001*
	M	18	0	0	1	5	9	3		
15 min.	C	19	0	0	0	3	3	13	-2.15	0.03*
	M	17	0	0	0	6	8	3		
30 min.	C	18	0	0	0	1	8	9	-0.33	0.74
	M	17	0	0	0	1	5	11		
45 min.	C	17	0	0	0	0	2	15	-3.05	0.002*
	M	14	0	0	1	2	2	9		
60 min.	C	10	1	0	0	1	2	6	-3.07	0.002*
	M	11	0	0	0	1	4	6		

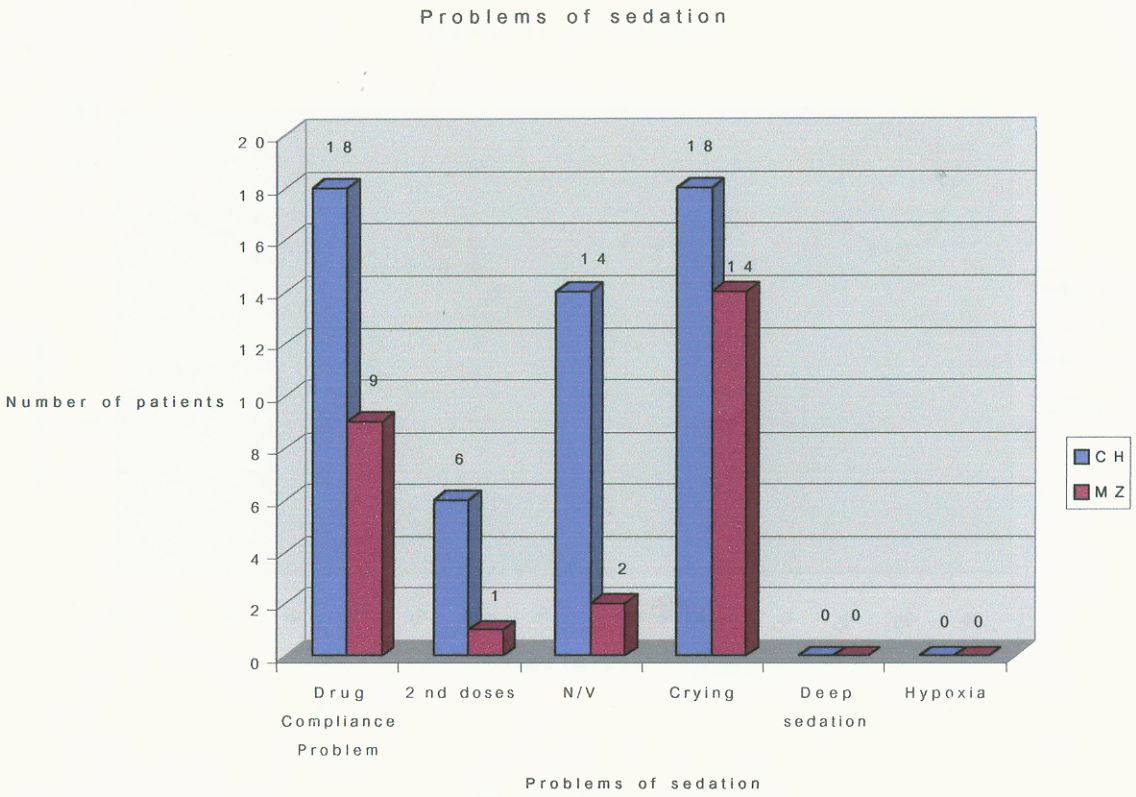
Problems of sedation
Number of patients
20
18
16
14
12
10
8
6
4
2
0
18
9
6
1
14
2
18
14
0 0
0 0
C H
M Z
Drug Compliance Problem
2 nd doses
N/V
Crying
Deep sedation
Hypoxia
Problems of sedation

Figure 1

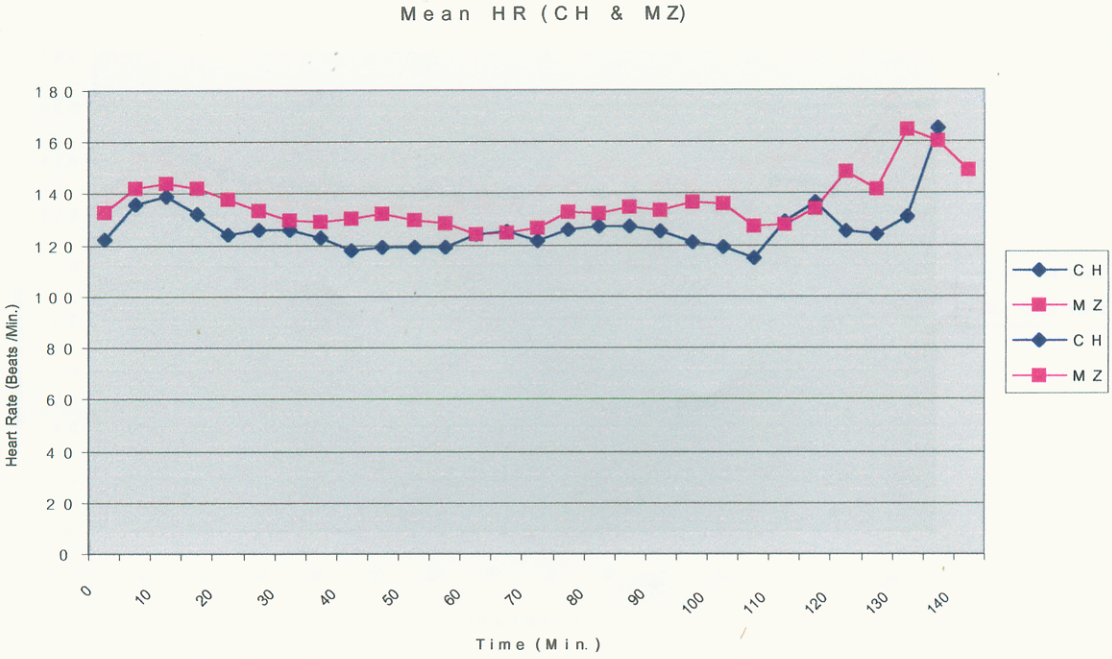
Mean HR (CH & MZ)
Heart Rate (Beats /Min.)
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
Time (Min.)
CH
MZ
CH
MZ

Figure 2

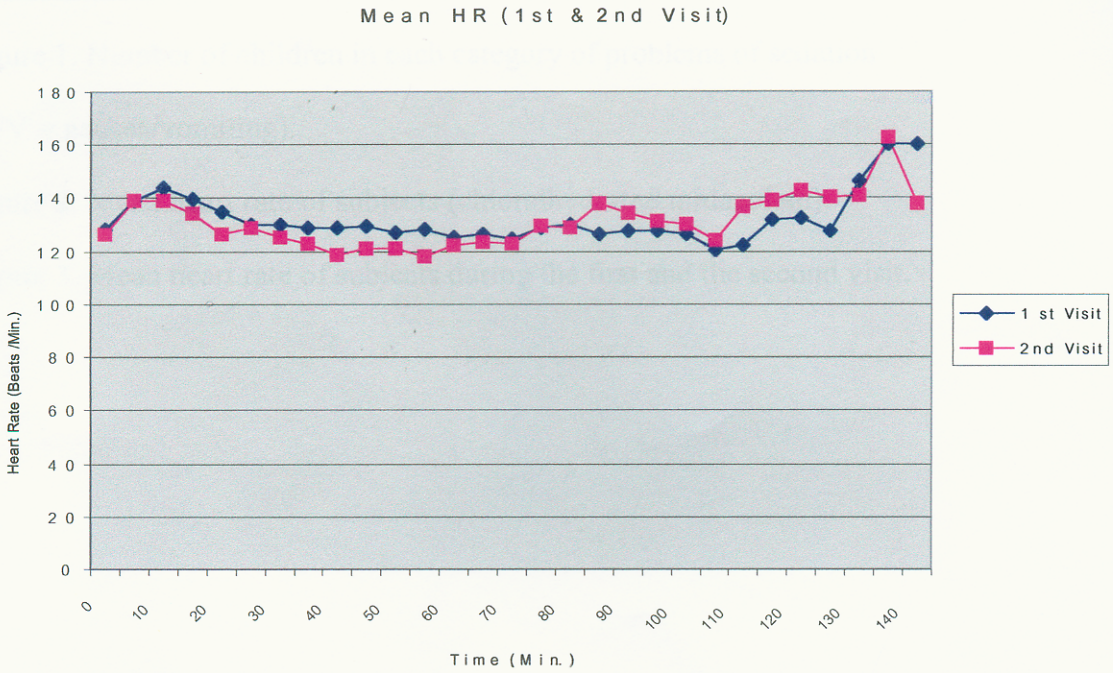
Mean HR (1st & 2nd Visit)
Heart Rate (Beats /Min.)
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
Time (Min.)
1 st Visit
2nd Visit

Figure 3

Figure Legends

Figure 1. Number of children in each category of problems of sedation (N/V = nausea/vomiting).

Figure 2. Mean heart rate of subjects (chloralhydrate&midazolam).

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