Comparison of Dexmedetomidine and Midazolam for conscious sedation in pediatric dental patients: A Clinical Randomized Trial

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Abstract: Objectives: The aim of this was study to assess and compare the effectiveness of two different sedation drugs (Dexmedetomidine and Midazolam) in the management of uncooperative pediatric dental patients. **Methods**: The study was performed on 30 children ranging in age from 4-8 years. The subjects were divided into two groups. Group "A" were premedicated with 2.5µgm/kg oral dexmedetomidine, while group "B" received 0.5mg/kg oral Midazolam. Child sedation level, as well as, behavior rating were assessed during treatment. Pulse rate, systolic blood pressure and oxygen saturation were monitored throughout treatment time. **Results**: the quality of sedation was better but not significantly different in dexmedetomidine when compared with midazolam. There was significant decrease in both heart rate and systolic blood pressure with dexmedetomidine, in comparison to baseline and to midazolam.**Conclusions**: Oral dexmedetomidine is comparable to oral midazolam in sedating child dental patient, with significant decrease in heart rate and blood pressure, when compared to oral midazolam.
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1.Introduction

The field of pediatric dentistry beholds the greatest challenge among the various other branches of dentistry in providing dental care without inflicting any adverse psychological impact upon the child.(1) Uncooperative behavior in the dental setting is most typically attributed to behavioral manifestations of anxiety; such uncooperative behavior has been rated by dentists as being the major problem in the dental chair. Major consequences of such uncooperative behavior may include a delay or termination of treatment before completion, or a decrease in the quality of care provided. (2)

Today modern pediatric dentistry describes so many techniques to manage the behavior of the child dental patient. The use of range of drugs as adjuvant to behavioral psychology should enable the dentist to handle most of unmanageable children.

The most common drug regimens and techniques are oral midazolam 0.5-0.75mg/kg, chloral hydrate 50-100mg/kg, and nitrous oxide/oxygen inhalation sedation.(3)Although commonly used, there are certain limitations with different regimens; Paradoxical reactions and prolonged sedation postoperatively are common with oral sedatives.(4-5)Other undesirable effects including restlessness, paradoxical reaction, and negative postoperative behavioral changes have made them a less than ideal premedication.(6-7)With inhalation sedation by nitrous oxide, it is difficult to achieve or maintain the desired sedated state if the patient keeps on crying or uncooperative with breathing through the nasal hood.(3)

In the last few years, a group of α 2-adrenoceptor agonists has been suggested as another option for premedication in children.(8-10) α2 receptors are found in the peripheral and central nervous systems, platelets, and many other organs, including the liver, pancreas, kidney, and eye. Stimulation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia.(11)

Unlike most sedative drugs, α 2 adrenoceptor agonists are capable of producing both sedation and analgesia and result in little-if any- respiratory change.(12) The quality of sedation produced by α2 agonists differs from sedation produced by drugs that act on GABA receptors such as midazolam; α2 agonists produce sedation by decreasing the sympathetic nervous system activity and the level of arousal, the result is a calm patient who can be easily aroused to full consciousness. Drugs that activate GABA receptors produce a clouding of consciousness and can cause paradoxical agitation as well as tolerance or dependence.(13)

Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in humans for analgesia and sedation.(14) In late 2008, the FDA approved the use of dexmedetomidine for

nonintubated patients requiring sedation prior to and/or during surgical and other procedures. [15]

Dexmedetomidine is a potent centrally acting α 2 agonist that has short half-life of 1.5–3 h so make it easier to titrate, quicker to recover, mimicking some aspects of natural sleep.[16-17]The drug was introduced two decades ago as a sedative and supplement to sedation in the intensive care unit for patients whose trachea was intubated.[18] Since then, it was widely adapted by anesthesiologists in the operating room. It has been used for sedation and analgesia in adults and pediatric patients undergoing small and minimally invasive procedures, with high safety and efficacy. [18-19]

Besides being administered through intravenous infusion, Dexmedetomidine was also used through intranasal[8,18-20] as well as oral administration[21] where it has proven to produce sedation in 45–60 min and peaks in 90–105 min, with only a modest reduction of heart rate (HR) and arterial blood pressure (BP).

The prospects of sedation and analgesia provided by one drug in single oral dose and excellent oral bioavailability of Dexmedetomidine prompted us to study its efficacy as premedication in pediatric patients and compare it with oral Midazolam, a gold standard premedication, in pediatric patients.

Aim of study

The aim of this study was:

To assess and compare the effectiveness of two different sedation regimens (Dexmedetomidine and Midazolam) in the management of uncooperative pediatric dental patients.

2.Material and methods

This was a prospective, randomized, observational study. With appropriate ethical approval, thirty children ranging in age from 4–8 years were enrolled in the study. Children were selected from those attending the outpatient dental clinic of the Department of Pediatric and Preventive Dentistry, Faculty of Dentistry, 6th of October University for Modern Science and Technology. They were selected according to the following criteria.

- Normal healthy children without systemic disease ASA physical status I (App. I)[23]
- No history of drug allergy, known or suspected airway problems, pulmonary disease, gastrointestinal disorders that affect drug absorption, or those on sedative medications.[24]
- No obesity problem (weight >95th percentile for age)
- Negative behavior ; child cooperation scores 1 or 2 according to Frankl Behavior Rating Scale (App. II)[25].
- Having a dental condition that needs local anesthetic injection.

After obtaining parental written informed consent, each child was subjected for complete medical examination, and scheduled for dental procedure. Fasting instruction were given to the parents (8 h with allowing clear fluids up to 2 h).[3]At the day of dental visit, children were weighted in kg and randomly assigned for one of the two groups:

Group A: 15 child receiving 2.5 µg/kg oral dexmedetomidine (Precedex. Dexmedetomidine HCL injection. 200mcg/ml. Hospira, Inc; Lake Forest, IL 60045 USA, Fig 1).

Group B: 15 child receiving 0.5 mg/kg oral midazolam(Dormicum, Hoffman La Roche Ltd. Bazel Switzerland, Fig 2).

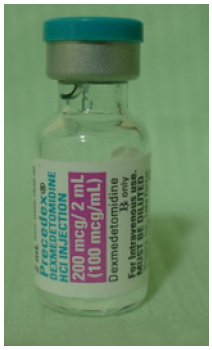

Fig (1): Precedex(dexmedetomidine) 200mcg/ml

Fig(2): Dormicum (midazolam) 5mg/5ml.

After preparing the sedative drug according to children body weight, the drug was suspended in a plain apple juice, to mask the bitter taste and make it more palatable for oral administration. The pulse oximeter (Nonin. Onyx. Nonin Medical, Inc, Plymouth, MN. USA, Fig 3) and blood pressure cuff were attached (Fig 4). Baseline parameters were recorded and the assigned drug was administered. The child was left with the accompanying parent for some time (60 min in group A, 30 min in group B) in

order to attain optimum sedation level. local anesthesia was administered, and dental treatment was performed. The dentist used local anesthesia with lidocaine (Mepecaine-L. Alexandria Co for Pharmaceuticals. Alexandria-ARE) 2% at a maximum dose of 4 mg/kg.[26] Patients were discharged when fulfill the discharge criteria (Steward Recovery score of 6) (App IIII)[27] and after informing the parent with the post sedation instructions (App IV).[24,28]

Fig (3): Pulse oximeter

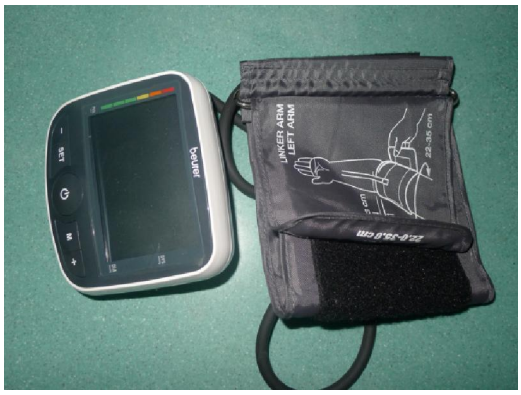

Fig (4): digital sphygmomanometer

All facilities for securing and maintaining a patent airway, providing O_2, artificial ventilation and cardiopulmonary resuscitation were available at all times. For each child, the following parameters were recorded:

- Patients' sedation status was scored according to Ramsey Sedation score (App V).[29] Assessment was performed by an independent observer blinded to the group assignment.
- Behavior was rated according to Modified Houpt scale for behavior rating (App. VI).[30] It was rated at baseline, after sedation, at local anesthetic injection and at the start of dental procedure.
- Hemodynamic response was monitored throughout the treatment sessions. Measurements included systolic blood pressures BP, heart rate HR and oxygen saturation saO_2.Measurements were recorded at baseline, optimum sedation, local anesthetic injection, and at 5 minute intervals throughout the dental procedures

Terminating operative time occurred at either the completion of all necessary work or upon the assessment of uncontrollable behavior.

Children were monitored for at least one hour following the procedure until discharge criteria were met.

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0.[31] .Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum). Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For abnormally distributed data, comparison between the two studied groups were done using Mann Whitney test. To compare between the different periods Wilcoxon signed ranks test was assessed. Significance of the obtained results was judged at the 5% level.[32]

3.Results

Demographic characteristics for all patients are summarized in table 1. Differences were not statistically significant with respect to age, weight, gender, type of procedure (pulpotomy PPt, extraction EXT, or cavity preparation CAV).

Table 2 shows sedation scale in both groups. Children who received dexmedetomidine were effectively sedated yet were easily arousable; a feature not observed with children of the midazolam group, who were disoriented and drowsy at all times. However, there was no significant difference between the two groups(p= 0.337).

Table (1): Comparison between Demographics of subjects in the two studied groups.

	Group A (n = 15)	Group B (n = 15)	*p*
Age (years)	61.0 (50.0 – 84.0)	71.0 (50.0 – 86.0)	0.245
Weight	19.0 (14.0 – 27.0)	22.0 (15.0 – 26.0)	0.466
Frankl	2.0 (1.0 – 2.0)	2.0 (1.0 – 2.0)	0.717
Gender			
Male	8 (53.3%)	8 (53.3%)	1.000
Female	7 (46.7%)	7 (46.7%)	
Treatment			
PPt	9 (60.0%)	7 (46.7%)	
EXT	4 (26.7%)	6 (40.0%)	0.875
CAV	2 (13.3%)	2 (13.3%)	

Qualitative data were described using number and percent and was compared using Chi square test, while abnormally quantitative data was expressed in Median (Min. – Max.) and was compared using Mann Whitney test.

Table (2):Comparison of sedation levels between the two studied groups according to Ramsey sedation scale.[29]

	Baseline	Optimum sedation
Group A	1.0(1.0 – 1.0)	5.0# (4.0 – 6.0)
Group B	1.0 (1.0 – 1.0)	5.0# (4.0 – 5.0)
	P= 1.000	*P*= 0.337

Abnormally quantitative data was expressed in Median (Min. – Max.) and was compared using Mann Whitney test.
#: significant with base line

Children in group "A" exhibited a more quiet behavior at all times throughout the treatment procedure, when compared to those of group "B". They showed a notably better tolerance of the anesthetic injections (absence or little crying or resistance). Although children of group "B" were more drowsy, they were resistive when dealing with painful moments such as injection. The differences were not statistically significant (p>0.0001) (Table 3).

Regarding the overall behavior of children. Three out of 15 child in group "A" scored 5(excellent overall behavior, no crying or movement), compared to only one child in group "B". The median score in group "A" was 4 (Good, some limited crying or movement), compared to 3(Fair, difficult, all treatment completed) in group "B". No significant difference was noted between the two groups. (Table 4).

Table (3):Comparison of behavior between the two studied groups according toModified Houpt Scale.[30]

		Base line	Optimum sedation	Injection	Treatment
Sleep	**Group A**	1.0 (1.0 – 1.0)	2.0# (2.0 – 3.0)	2.0# (2.0 – 2.0)	2.0# (2.0 – 3.0)
	Group B	1.0 (1.0 – 1.0)	2.0 # (1.0 – 3.0)	2.0# (2.0 – 2.0)	2.0# (3.0 – 3.0)
	p	1.000	0.095	1.000	0.550
Body movement	**Group A**	2.0 (1.0 – 4.0)	4.0# (2.0 – 4.0)	3.0# (2.0 – 4.0)	3.0# (2.0 – 4.0)
	Group B	3.0 (1.0 – 4.0)	3.0# (2.0 – 4.0)	3.0 (1.0 – 3.0)	3.0# (2.0 – 4.0)
	p	0.731	0.269	0.085	0.317
Head/oral resistance	**Group A**	3.0 (1.0 – 4.0)	3.0 (2.0 – 4.0)	4.0 (1.0 – 4.0)	4.0# (3.0 – 4.0)
	Group B	3.0 (1.0 – 4.0)	3.0 (1.0 – 4.0)	4.0 (1.0 – 4.0)	4.0# (3.0 – 4.0)
	p	0.982	0.740	0.914	0.369
Crying	**Group A**	4.0 (1.0 – 4.0)	4.0 (2.0 – 4.0)	3.0 (2.0 – 4.0)	3.0 (1.0 – 4.0)
	Group B	4.0 (2.0 – 4.0)	3.0# (1.0 – 4.0)	3.0# (1.0 – 4.0)	3.0# (1.0 – 4.0)
	p	0.457	0.209	0.736	0.289
Verbal	**Group A**	4.0 (2.0 – 4.0)	4.0 (2.0 – 4.0)	3.0# (2.0 – 4.0)	4.0 (3.0 – 4.0)
	Group B	3.0 (1.0 – 4.0)	3.0 (1.0 – 4.0)	3.0 (2.0 – 4.0)	3.0 (2.0 – 4.0)
	p	0.193	0.436	0.417	0.082

Abnormally quantitative data was expressed in Median (Min. – Max.) and was compared using Mann Whitney test.
#: significant with base line

Table 4. Comparison of the overall behavior between the two studied groups, according to Modified Houpt Scale.[30]

	Overall behavior	*p*
Group A	4.0 (2.0 – 5.0)	0.279
Group B	3.0 (2.0 – 5.0)	

Abnormally quantitative data was expressed in Median (Min. – Max.) and was compared using Mann Whitney test.

Results of hemodynamic response:

Table 5 describes oxygen saturation in both groups. It did not change in any group during the course of the study, and there wasn't any significant difference between the two groups. There were no episodes of oxygen desaturation below 95% at any time in both groups.

Table 5: Comparison of oxygen saturation between the two groups.

	Base line	Optimum sedation	Injection	5 min	10 min	15 min	20 min
Group A	99 (98 – 100)	99 (98 – 100)	100 (98 - 100)	99 (96 - 100)	100 (95 - 100)	100 (95 - 100)	99 (95 - 100)
Group B	100 (95 – 100)	99 (97 - 100)	98 (97 - 100)	99 (96 - 100)	99 (97 - 100)	99 (95 - 100)	100 (98 – 100)
p	0.875	0.687	0.056	0.912	0.725	0.929	0.457

Abnormally quantitative data was expressed in Median (Min. – Max.) and was compared using Mann Whitney test.
#: significant with base line

Comparison of heart rate between the two groups showed a significant decrease in children of group "A" compared to group "B", this was significant at all times during procedures it decreased by 11%. (Fig 5). However, there were no clinically significant episodes of bradycardia or hypotension (values < 2 sd for age) in the two groups likewise, comparison of sBP between the two groups showed significant decrease in group "A" compared to group "B" at all times (p=0.001, 0.002, 0.002, 0.002, 0.002 and 0.004). Overall, there was significant decrease of systolic blood pressure in children of group A in comparison with baseline at all recordings (p<0.05).(Fig 6)

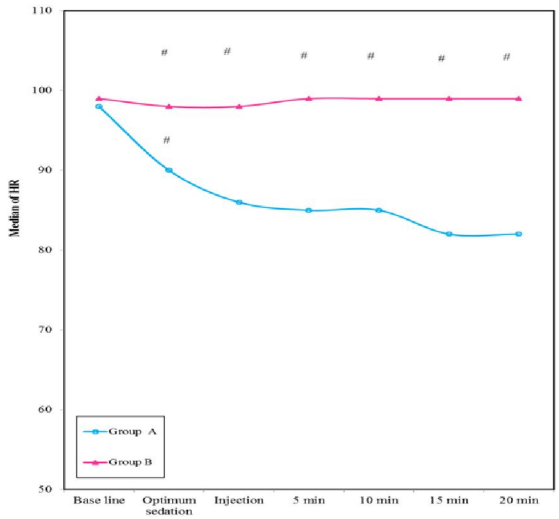

Fig (5): Comparison of HR between the two study group along time

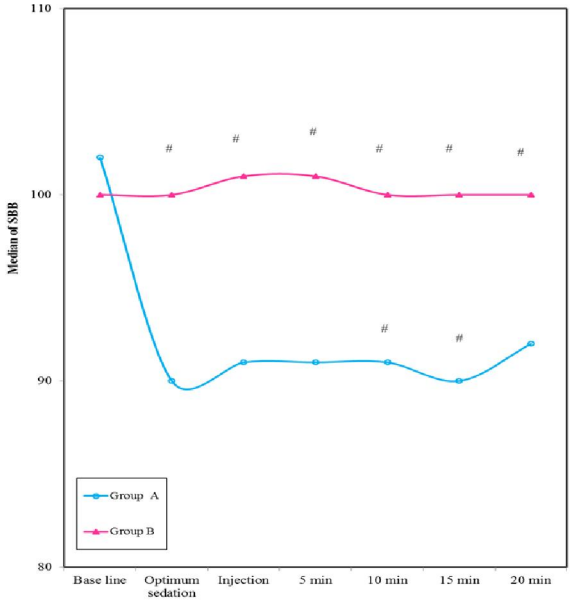

Fig (6): Comparison of sBP between the two study group along time

4. Discussion

Sedation for pediatric dental treatment presents special challenges. Although complete immobility is not required, the patient must be cooperative and relatively still, must maintain protective airway reflexes, and must allow the operator to work intraorally.

An ideal sedative for pediatric outpatient dental procedures would be effective, easy to administer, have a rapid onset, and be inexpensive. Most importantly, it would carry minimal risk of

cardiorespiratory depression or prolonged CNS depression. These are some of the characteristics that dexmedetomidine proved to possess. Despite these excellent attributes, there seems to be very little information in the literature on using oral dexmedetomidine for pediatric patients undergoing dental treatment.[33]

The results of our preliminary study indicate that oral dexmeditomedine2.6 mg/kg , provides high-quality sedation for young children undergoing outpatient dental procedures, comparable to that provided by midazolam.

Although children of both groups were comparably sedated as shown by sedation Ramsey scores, with no significant difference noted, behavior was notably different between the two groups. The inconsistency between sedation scores and behavior scores may be attributed to the unique nature of dental treatment session that makes most sedation scales used by anesthetist not suitable for such settings; Sedation level required for parental separation or anesthetic induction is not that adequate for keeping a combative child quiet and cooperative on the dental chair.

Behavior scales are more effective in assessment of sedation regimens used for dental treatment. In the present study, the Modified Houpt scale was used, as it accurately assesses the child behavior that has a direct influence on the progress of treatment. Although not significant, the children premedicated with Dexmedetomidine exhibited more quiet attitude and less crying and struggling when compared to those received Midazolam. (tables 3,4) with midazolam, 3 out of 15 children did not complete the intended treatment procedure because of uncontrollable behavior, compared to one child sedated with dexmedetomidine. The lack of significance may be attributed to the small sample size.

Similar findings were reported by Schmidt et al.[34]The authors reported that premedicating children with 1 mcg/kg transmucosal dexmedetomidine resulted in less perioperative sympathetic stimulation and postoperative pain as compared to children who were given 0.5 mg/kg oral midazolam.

This is consistent with the results of a previous study by Hall *et al.*[35]who reported that α2 agonists behave differently from other sedatives, seemingly producing something closer to sleep, and yet gaining a level of consciousness sufficient to gain compliance with orders which is considered a unique characteristic of α2 Agonist sedation. However we cannot rule out the possibility that the lower sympathetic tone produced by Dexmeditomedine and not the deeper sedation level, might have contributed to the less struggling behavior of children.

Regarding the hemodynamic response, Dexmedetomidine showed significant reduction in HR at all times in comparison with baseline (8.1-16.3%), this was significantly different than the effect of midazolam, which has minimal effect on heart rate except a modest reduction at optimum sedation. These results are coincident with previous studies [8,36-38] which reported that dexmedetomidine causes a dose-dependent decrease in HR. However, Most of these studies reported greater decrease in heart rate (14% to 27 %). This inconsistency may be due to the different nature of procedures; In these studies, Dexmedetomidine was tested as a premedication before induction of anesthesia, while in the present study, the environment of the dental treatment makes the child more alert and responding to the continuous oral stimulation.

The significant difference between the two groups can be attributed to the known sympatholytic action of dexmedetomidine with the added analgesic effect that decreases crying in painful moments more than did midazolam. (intermittent crying in group B with injection and painful moments may have contributed to this significant difference as midazolam doesn't have the analgesic effect of dexmedetomidin).

The results of blood pressure shows a significant decrease in sBP with dexmedetomidine, which is considered a well known effect of the drug. This hypotensive effect was of benefit in gaining more calm behavior in group "A". Similar results were reported in previous studies [36-39]. These effects have minimal clinical significance and can only be deleterious in hypovolemic patients or patients with fixed stroke volume.[40] On the other hand, midazolam shows significantly more stable blood pressure at all times, when compared to dexmedetomidine. A stable hemodynamic response has been reliably expected with midazolam sedation in most published studies. [40]

In most published studies,[41-43]any sedation regimen that allows a procedure to be completed is counted as successful. The present study documented a new oral sedative that can be used successfully in sedating child dental patients.

Conclusions

- Oral dexmedetomidine is comparable to oral midazolam in sedating child dental patient.
- Oral dexmedetomidine sedation results in significant decrease in heart rate and blood pressure, when compared to oral midazolam

Recommendations

Further studies are needed to assess different dosages of oral dexmedetomidine as sedation drug in pediatric dentistry

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APPENDIX I

American society of Anesthesiologists physical status classification (ASA)[22]

class I.A normally healthy patient with no organic, physiologic, biochemical or psychiatric disturbance, or disease.

class II. A patient with mild-to-moderate systemic disturbance or disease that does not affect their lifestyle.

class III. A patient with severe systemic disturbance or disease that limits activity but is not incapacitating.

class IV. A patient with severe incapacitating systemic disease or disorder that is a constant threat to life.

class V. A moribund patient not expected to survive 24 hours, with or without medical intervention.

class VI.A clinically brain-dead patient awaiting organ retrieval surgery.

Appendix (II)

Frankl Behavioral Rating Scale.[24]

Rating 1: Definitely negative

Refusal of treatment, crying forcefully, fearful, or any other overt evidence of extreme negativism.

Rating 2: Negative

Reluctant to accept treatment, uncooperative, some evidence of negative attitude but not pronounced (sullen, withdrawn).

Rating 3: Positive

Acceptance of treatment: at times cautious; willingness to comply with the dentist, at time

reservation, but patient follows the dentist's directions cooperatively.

Rating 4: Definitely positive

Good rapport with the dentist, interested in the dental procedure, laughing and enjoying.

Appendix (III)

Steward Recovery score[27]

Consciousness	**2**	Consciousness
	1	Responding to stimuli
	0	Not responding
Airway	**2**	Coughing on command or crying
	1	Maintaining good airway
	0	Airway requires maintenance
Movement	**2**	Moving limbs purposefully
	1	Non purposeful movements
	0	Not moving

Appendix (IV)

Post sedation instructions[24,28]

- It is expected that your child may sleep for several hours the day of the procedure, and may remain drowsy for the rest of the day.
- Close observation of your child is mandatory for the rest of the day. He/she should never be left unattended.
- Do not allow your child to play near streets, stairways, and other areas where he/she may be injured by falling, for the rest of the day.
- Transportation by car safety seat poses a risk for the child.
- Carefully observe the child's head position, it should remain in a reclined position, so as to avoid air obstruction.
- Activities should be limited for the rest of the day.
- Cold drinks will help reduce any nausea and stimulate your child to be more alert
- Do not allow the child to bite his/her lip, tongue or check, if a local anesthesia has been used.
- Should any unusual situation arise, please call at the given phone number as soon as possible.

Appendix (V)

Ramsey Sedation Scale [29]

Score	Response
1	Anxious or restless or both
2	Cooperative, oriented and tranquil (calm)
3	Responding to command
4	Brisk (quick) response to stimulus
5	Sluggish (slow moving) response to stimulus
6	No response to stimulus

Appendix (VI)

Modified Houpt scale for behavior rating[30]

Sleep

1. Awake,alert
2. Drowsy, disoriented
3. Intermittently asleep
4. Sound asleep

Body movement

1. Violent, uninterrupted movement
2. Continuous, making treatment difficult
3. Controllable, does not interfere with treatment
4. No body movement present

Head/oral resistance

1. Turns head, refuses to open mouth
2. Mouth closing, must request to open
3. Chocking, gagging, spitting
4. No head/oral resistance present

Crying

1. Hysterical, demands attention
2. Continuous, making treatment difficult
3. Intermittent, mild, does not interfere with treatment
4. No crying present

Verbal

1. Verbal abuse, threats
2. Verbal protest
3. Statement of discomfort
4. Occasional talking or silence

Overall

1. Aborted, no treatment performed
2. Very poor, treatment interrupted, partial treatment completed
3. Fair, difficult, all treatment completed
4. Good, some limited crying or movement
5. Excellent, no crying or movement

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