

INTRAVENOUS CONSCIOUS SEDATION IN UNCOOPERATIVE CHILDREN UNDERGOING DENTAL PROCEDURES: A COMPARATIVE EVALUATION OF MIDAZOLAM/ PROPOFOL AND KETAMINE/ PROPOFOL

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ABSTRACT

There is a lack of clinical trials on pediatric dental sedation. We investigated efficacy of intravenous conscious sedation during dental treatment with Midazolam/ Propofol compared to Ketamine / Propofol in 4-6 years old children. In this prospective clinical trial study 38 healthy non-cooperative children candidate dental treatment under Intravenous conscious sedation randomly were divided into two groups. Intravenous conscious sedation in one group was performed by midazolam/ Propofol and in the other group carried out by Ketamine /propofol. The bispectral index and sedation score from Dental Sedation Teachers Group (DSTG) was employed for evaluating the sedation effect of each regimen by a one trained, blinded observer. The working conditions for each patient were assessed at the end of the treatment, using the rating scale by DSTG and the time taken to achieve discharge criteria was also recorded. Data analysis was performed using, variance analysis test for repeated data Friedman, Mann-Whitney and T- Test. Good sedation of the 2 groups after intravenous administration was observed. In midazolam/propofol group BIS index was higher than ketamine/ propofol group but there was no statistical difference for sedation BIS index (PV=0.153). There was no statistical difference for sedation score, working condition and recovery time between children receiving midazolam/ propofol or ketamine/ propofol (PV>0.05). Midazolam/ Propofol and Ketamine / Propofol, intravenous conscious sedation is efficacious for guiding the behavior of 4-6 years old children during dental treatment.

KEYWORDS: Intravenous, Conscious Sedation, Midazolam, Propofol, Ketamine

Treatment of an uncooperative pediatric patient is extremely difficult in dentistry (1-3). Behavior management alone is not always sufficient for cooperation; therefore there is a need for sedation or general anesthesia. Various sedative agents and combinations have been used to reduce the anxiety and fear associated with dentistry, but variable results have been obtained with respect to efficacy and safety (4).

Midazolam is an example of such a sedative agent. As a water-soluble benzodiazepine, midazolam is nonirritating and has anxiolytic, sedative, hypnotic, and amnesic properties (5).

It has also been suggested that the drug has a mild analgesic effect resulting from the central suppression of pain perception (6). Ketamine, a phencyclidine derivative, is a rapidly acting, non-narcotic, non-barbiturate drug with a wide margin of safety (7). These actions produce a unique combination of sedation, amnesia, and analgesia making this drug ideal for outpatient procedures (8). Propofol is an alkylphenol solubilized in different lipids and at

concentrations of 1% and 2%. At low doses it produces conscious sedation, while at higher doses it produces deep sedation and anesthesia (9). Propofol has a pharmacokinetic profile leading to rapid induction and recovery times with minimal postoperative confusion (10).

In the hands of properly trained professionals, intravenous conscious sedation can be the easiest, most efficient, and safest method (11). Among the parenteral routes, only the intravenous route allows exact titration to a desired drug effect (12). There are basically two techniques for using intravenous sedation. The first employs a single drug, whereas the second requires a sophisticated combination of several drugs. A goal of combining agents should be to establish a balance between sedation, analgesia, and amnesia, all while minimizing adverse effects and maintaining physiologic homeostasis. When agents are combined, often one drug will be potentiated by another. Their combination thus enables the operator to reduce the dosage of a stronger drug, and thus reduce the possibility or degree of an adverse effect (11).

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The bispectral index (BIS) system uses processed electroencephalographic signals to measure sedation on a unitless scale from 0 to 100 (with 0 indicating coma and 100 indicating normal). The BIS has been validated with children undergoing general anesthesia in the operating room (13-17).

Outside the operating room, McDermott et al (18) found the BIS monitor to correlate well with the University of Michigan Sedation Scale and to be a valid measure of the level of sedation.

Unfortunately; very little study existed in combination of drugs in intravenous conscious sedation pediatric dentistry. The goal of this study is to evaluate the efficacy of combination Midazolam and Propofol versus combination of Ketamine and Propofol in 6-8 years old children during intravenous conscious sedation dentistry.

MATERIALS AND METHODS

This prospective, randomized, double-blind, clinical trial study was approved by the Research Ethics Board of the Isfahan University of Medical Sciences. The parents were asked to sign a written informed consent after being informed about the aims, procedures, risks, and benefits of the study.

Sample

38 patients referred from pediatric dental services to dental sedation clinic selected. This trial was performed in operating room at the School of Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran.

Patients who meet any of the following criteria were included in this study: 1) children who are 4 to 6 years of age, 2) children who are ASA I, 3) no mental or physical deficiency, 4) Frankel Rating 2: Negative (Reluctance to accept treatment, uncooperativeness, some evidence of negative attitude but not pronounced, sullen, withdrawn) (19), 5) children who need any dental treatment except extraction on the posterior region of the upper jaw. Exclusion criteria were known allergy to Midazolam, Ketamine, Propofol and/or lidocaine or a history of serious adverse events with these drugs, parent's refusal, medical complications during treatment and a history of

Spontaneous pain of the posterior maxillary teeth due to severe infection.

Study Procedure

All the children were examined by anesthesiologist and received similar directions. The children divided into two groups by stratified random selection method. After taking the weight, the patient was transferred to the operating room and catheterized on the hand by the means of an Angiocath 22 gauge catheter (Mediplus, India) and received either of the following two regimens:

1. In group Midazolam/ Propofol (n=18): Sedation was introduced with a single bolus of i.v. midazolam (Tehran Chemie Pharmaceutical co, Iran) 0.05 mg /kg, followed by infusion of propofol (Dongkookpharma Co, Korea) 0.5 mg /kg /h up to the end of the procedure.
2. In group Ketamine / Propofol (n=18): Sedation was introduced with a single bolus of i.v. ketamin (Rotex Medical, Germany) 0.5 mg /kg, followed by infusion of propofol (Dongkookpharma Co, Korea) 0.5 mg /kg /h up to the end of the procedure.

All patients monitored with pulse-oxymeter which shows respiratory rate, heart rate, saturation and blood pressure. Any incidence of desaturation or hypotension was managed by giving oxygen through nasal prong or fluids and vasopressors, respectively, while excluded from study.

Dental treatment was performed by one pediatric dentist who was blinded to study drugs. All children received 2% lidocaine with 1:80,000 epinephrine as local anesthetic (Daroupakhsh®, Iran), at a maximum dose of 4.4 mg/kg, for maxillary infiltration. In the recovery room children were monitored until they met the discharge criteria (11): cardiovascular function and airway patency satisfactory and stable, child easily arousable and with protective reflexes intact, child could talk, child could sit up unaided, child met the pre-sedation level of responsiveness as closely as possible and adequate state of hydration. Time taken to achieve these criteria was noted as recovery time.

On the day after the dental sedation treatment, a member of research team called the accompanying adult of each children to find out about any adverse event.

Measurement

The sedation and operating conditions, was assessed by one trained, blinded observer throughout the treatment using a sedation score and assessment of operating conditions adapted from Dental Sedation Teachers Group (DSTG), as used elsewhere(20).

In this measurement, the sedation scoring is, 1 = fully awake and oriented, 2=drowsy, 3=eyes closed, responds promptly on verbal command, 4= eyes closed, rousable on mild physical stimulus, 5= eyes closed, unrousable on mild physical stimulus. A sedation score was assessed at the following moments during the treatment: 5 minutes after beginning of the sedation, 15, 30 and 45 minutes after beginning of the dental operation. The observer was instructed to report the highest sedation score in each assessment moment. Another observer recorded the BIS scores (Aspect Medical System, Inc, USA) at the same times.

At the end of the treatment, the working conditions assessed by: 1=patient fully cooperative with optimum degree of sedation (good), 2= minimal interference from patient due to over/under sedation (fair), 3=operating difficult due to over/under sedation (poor), 4=action taken (impossible). And the time taken to achieve discharge criteria was also recorded as recovery time.

Data Analysis

Using the Mann-Whitney U test, the difference in

the sedation score was evaluated.

Data analysis was performed using variance analysis test for repeated data, Friedman and T-Test.The minimum P-value for being meaningful was assumed 0.05 and for the confidence coefficient it was assumed 95%.

RESULTS

38 subjects including 17 girls (44.7%) and 21 boys (55.2%) included in this study. The mean age of patient's was 5.34 ± 0.71 . There were no differences between the participant's average age, sedation time and sex between 2 groups using T-test (Table-1).

Average BIS index in the midazolam/propofol group 5 minutes after beginning of the sedation was 84.79 ± 4.63 which revealed an increase during sedation and finally reached 89.43 ± 2.76 . The ketamine/ propofol group had an average BIS index 83.16 ± 5.65 , which increased to 87.83 ± 3.25 , 45 minutes after beginning of the sedation (diagram 1 and table 2). In midazolam/propofol group BIS index was higher than ketamine/ propofol group in all four stage, but there was no statistical difference for sedation BIS index between children receiving midazolam/ propofol or ketamine/ propofol using the variance analysis test for repeated data ($PV=0.153$). In both groups, the average BIS index had a statistically meaningful increase in all 4 stages using the variance analysis test for repeated data ($P<0.05$).

Mean sedation score in the midazolam/propofol

Table 1: Average Age, Sedation Time and Sex in Study Groups.

Group	Age	Male	Female	Sedation Time
m/p		10	9	38.42 ± 6.46
k/p	5.47 ± 0.71	11	8	36.32 ± 7.78
pv	0.68		0.08	0.371

Table 2: Average BIS Index in Different Stages of Study

Group	Average BIS index after 5 minutes after beginning of the sedation	Average BIS index after 15 minutes after beginning of the dental operation	Average blood BIS index 30 minutes after beginning of the dental operation	Average BIS index 45 minutes after beginning of the dental operation	P-value
midazolam/propofol	84.79 ± 4.63	86.95 ± 4.46	88.67 ± 2.74	89.43 ± 2.76	$P<0.001$
ketamine/propofol	83.16 ± 5.65	83.79 ± 3.29	87.16 ± 3.53	87.83 ± 3.25	$P=0.004$

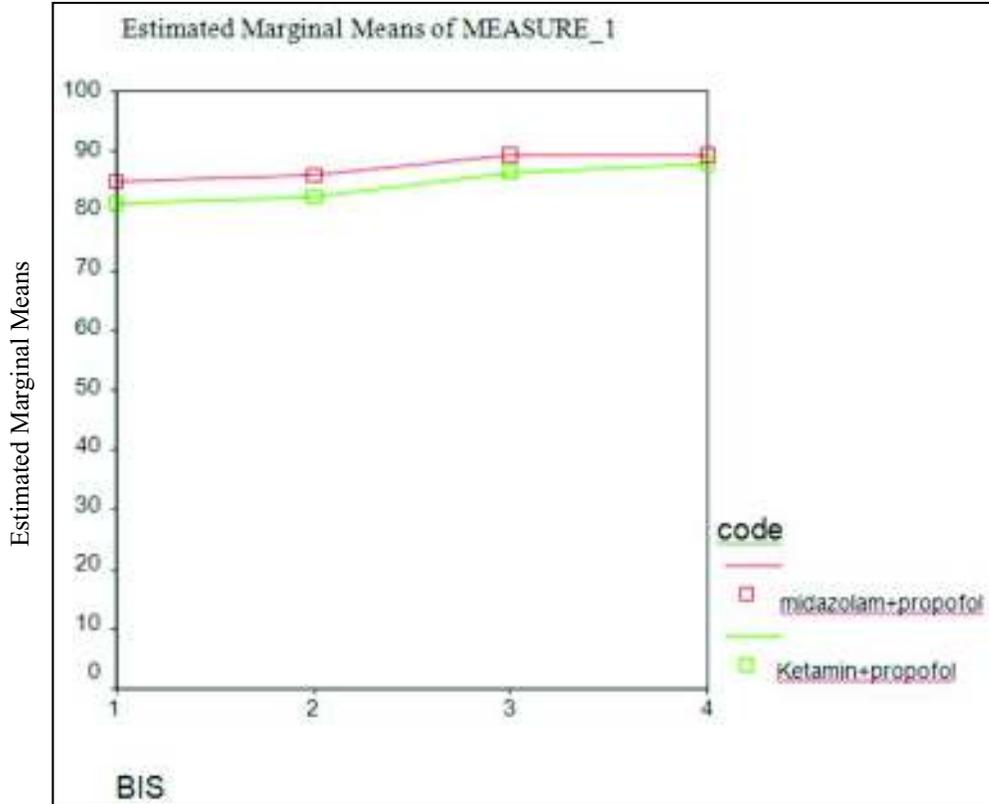


Table 3 : Mean Sedation Score in Different Stages of Study.

Group	Mean sedation score after 5 minutes after beginning of the sedation	Mean sedation score after 15 minutes after beginning of the dental operation	Mean sedation score 30 minutes after beginning of the dental operation	Mean sedation score 45 minutes after beginning of the dental operation	P-value
Midazolam/propofol	3.05	2.32	2.28	1.86	P=0.001
Ketamine/propofol	3.11	2.37	2.2	1.8	P=0.012

group 5 minutes after beginning of the sedation was 3.05, which revealed a decrease during sedation and finally reached 1.86. The ketamine/ propofol group had a sedation score 3.11, which decreased to 1.8, 45 minutes after 45 minutes beginning of the sedation (table3). In both groups, the mean sedation score had a statistically meaningful

decrease in all 4 stages using the Friedman Test ($P < 0.05$). Mann-Whitney Test, showed that there was no statistical difference for sedation score between children receiving midazolam/ propofol or ketamine/ propofol in all 4 stage ($PV > 0.05$).

To assess the impact of sedation appointments

onworking conditions, a Mann-Whitney analysis was used. No significant relationship was found between working conditions and sedation regimens using Mann-Whitney test ($P=0.639$).

The mean recovery time from the administration of drugs was 31.84 ± 8.368 minutes for midazolam/propofol and 32.11 ± 7.325 minutes for ketamine/propofol. There was no statistical difference for recovery time between children receiving midazolam/propofol or ketamine/propofol by using T-Test ($PV=0.918$).

Neither psychotomimetic effects nor other adverse events, such as vomiting, excessive sleepiness, paradoxical reaction and respiratory depression, were observed while the child was in dental office and recovery room.

DISCUSSION

There is a growing need for the use of sedative drugs in controlling highly uncooperative pediatric dental patients, which could rise cooperation and ease dental procedures. According to the results of this study, the rate of successful sedation during dental treatment with either routes of midazolam/propofol administration was the same as ketamine/propofol. Midazolam is widely known as an effective sedative agent for many medical and dental procedures (21-28). Rai Ket al. studied (29) the efficacy and safety of conscious sedation, using intravenous short acting group of drugs (midazolam, propofol and ketamine) in uncooperative children. Result showed that propofol was highly effective in terms of onset of sedation, although increased body movements and crying, pain on injection and intermittent cough was observed as the main side effects of the drug. Midazolam showed the longest duration of action, but was not very effective in terms of treatment completion due to increased movements and crying. Maximum cooperation during the procedure was obtained with ketamine and no adverse effects were encountered. They preferred ketamine and recommended future evaluation of ketamine in combination with other sedatives. In our study, BIS index in K/P group was lower than M/P group in all four stage, that is showed, the children received K/P were more sedate than M/P, but there was no statistical difference for sedation BIS index between children

receiving midazolam/propofol or ketamine/propofol.

Arya VS et al. (30) evaluate and compare the efficacy and safety of Propofol and Midazolam as Intravenous sedative agents in the management of uncooperative children belonging to age group 2-5 years. The results showed both agents to be effective sedative agents, for short pedodontic procedures with minimal side effects. Shah A et al. (31) compared, ketamine/propofol with ketamine alone for pediatric, orthopedic procedural. The result showed that combination of ketamine and propofol produced slightly faster recoveries while also demonstrating less vomiting, higher satisfaction scores, and similar efficacy and airway complications. In our study, the recovery time in K/P was slightly longer than M/P, but there was not any statistical difference between two groups. It showed that for decrease recovery time of ketamine we can use it with propofol

Hosey MT et al. (32) evaluated Propofol intravenous conscious sedation for 34 anxious children in a specialist paediatric dentistry unit. In this study, Thirty-two children successfully accepted operative dental care on their first visit, they received a mean total dose of 146.25 mg of propofol (range 10 mg to 356 mg); in relation to body weight, the mean was 2.5 mg/kg (range 0.2-5.4 mg/kg). Alexopoulos E et al. (33), evaluated on two separate child sedation cohorts; one undergoing propofol intravenous sedation (IVS) and the other, nitrous oxide inhalation sedation (IS) in respect to changes in dental anxiety and subject characteristics. There were significant anxiety reductions within each procedure ($p < \text{or} = 0.001$) but there was no significant difference in the reduction of the self-reported anxiety scores between two procedure. The observed behavior was good for both cohorts. Finally they concluded that, Propofol target-controlled intravenous sedation and nitrous oxide inhalation sedation were similarly efficacious at anxiety reduction in referred dentally anxious children and further propofol conscious sedation studies are required. Veerkamp JS et al. (34), studied dental treatment of 19 toddlers under intravenous propofol sedation. Results suggested that sedation is difficult to achieve in young children. Recommendations for further research are made. In our study the use of

propofol was good for sedation of uncooperative children and we have no adverse effect of it.our finding support the use of Midazolam/ Propofol and Ketamine / Propofol, intravenous conscious sedation for guiding the behavior of children 4 to 6 years of age, undergoing dental treatment. The use of K/P was slightly better than M/P, but there were any statically differences. Further pragmatic studies with larger sample size are required to clarify the cost-effectiveness and safety of these procedures.

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REFERENCES

- Agudelo S. C., Mencía S., Faro A., Escudero V., 2012. [Continuous propofol perfusion in critically ill children]. *Med Intensiva*. 2012 Aug-Sep; 36(6):410-5. Epub Jan 13. Spanish.
- Alexopoulos E., Hope A., Clark S.L., McHugh S., Hosey M.T., 2011. A report on dental anxiety levels in children undergoing nitrous oxide inhalation sedation and propofol target controlled infusion intravenous sedation. *May;57(5):425-3*
- Arya V. S. and Damle S. G., 2002. Comparative evaluation of Midazolam and Propofol as intravenous sedative agents in the management of uncooperative children. 2002 Mar; 20(1):6-8.
- Bannister C. F., Brosius K. K., Sigl J. C., Meyer B. J., Sebel P. S., 2001. The effect of bispectral index monitoring on anesthetic use and recovery in children anesthetized with sevoflurane in nitrous oxide. *Pediatr Anesth*. 92 :877-881
- Bui T., Redden R. J., Murphy S., 2002. A comparison study between ketamine and ketamine-promethazine combination for oral sedation in pediatric dental patients. *AnesthProg winter; 49(1):14-8*.
- Campbell R. L., Ross G. A., Campbell J. R., Mourin A. P., 1998. Comparison of oral chloral hydrate with intramuscular ketamine, meperidine, and promethazine for pediatric sedation preliminary report. *AnesthProg*. 1998; 45:4650.
- Cathers J. W., Wilson C. F., Webb M. D., Alvarez M. E., Schiffman T., Taylor S., 2005. A comparison of two meperidine/hydroxyzine sedation regimens for the uncooperative pediatric patient. *Pediatr Dent*. ; 27:395-400.
- Chen J. W., Seybold S. V., Yazdi H., 2006. Assessment of the effects of 2 sedation regimens on cardiopulmonary parameters in pediatric dental patients: A retrospective study. *Pediatr Dent*. ; 28:3506.
- Coulthard P., Rood J. P., 1993. Objective measurement of the analgesic effect of midazolam in humans. *AnesthProg*; 40:35-38.
- Davidson A. J., Auble S. A., Sullivan L. J., Laussen P. C., 2000. The bispectral index in infants and children [abstract]. *PediatrAnesthesiol*.;93(3A):A1283.
- Denman W. T., Swanson E. L., Rosow D., Ezbicki K., Connors P. D., 2000. Rosow CE. Pediatric evaluation of the bispectral index (BIS) monitor and correlation of BIS with end-tidal sevoflurane concentration in infants and children. *Anesth Analg*. 90:872-877.
- E. R, Donald. Mc, Avery. D. R., 2011. *Dentistry for child and adolescent*. USA: Mosby Louis; P.31.
- E. R, Donald. Mc, Avery. DR. *Dentistry for child and adolescent*. USA: Mosby Louis; 2011. Ch 14. P253-276.
- Gustafsson A., Broberg A., Bodin L., Berggren U., Arnrup K. Dental behaviour management problems: The role of child personal characteristics. *Int J Paediatr Dent*. 2010; 20:24253.
- Gustafsson A., Broberg A., Bodin L., Berggren U., Arnrup K., 2010. Dental behaviour management problems: The role of child personal characteristics. *Int J Paediatr Dent*. ; 20:24253.
- Hosey M. T., Makin A, Jones R. M., Gilchrist F., 2004. Propofol intravenous conscious sedation for anxious children in a specialist paediatric dentistry unit. *Jan; 14(1):2-8*.
- Ingersoll B., 1982. *Behavioral Aspects in Dentistry*. New York, Appleton-Century Crofts; 107-127.

- Kaviani N., Jafarzadeh M, Mouhseni P., 2007 Evaluation of the effect of oral midazolam on non-cooperative children behavior control in pediatric dentistry. *Journal of Iranian society of Anesthesiology & Intensive care.*; 2(4):43-51
- Lam C, Udin R. D., Malamed S. F., Good D. L., Forrest J. L., 2005. Midazolam premedication in children: a pilot study comparing intramuscular and intranasal administration. *AnesthProg.* 2005 summer; 52(2):56-61.
- McDermott N. B., Van Sickle T., Motas D., Friesen R. H., 2003. Validation of the bispectral index monitor during conscious and deep sedation in children. *Anesth Analg.*;97 :39-43
- Milgrom P., Weinstein P., Kleinknecht R., Getz T., 1985. *Treating Fearful Dental Patients.* Reston, Virginia, Reston Publishing Co.
- Mizrak A., Erbagci I., Arici T., Ozcan I., 2010. Ketamine versus propofol for strabismus surgery in children. *ClinOphthalmol.*; 4:673-9.
- Pinkham J. R., 2013. Pediatric dentistry infancy throughout adolescence.; 8: 114.5ed.
- Rai K., Hegde A. M., Goel K., 2007. Sedation in uncooperative children undergoing dental procedures: a comparative evaluation of midazolam, propofol and ketamine. *Fall*; 32(1):1-4.
- Roelofse J. A., Louw L. R., Roelofse P. G., 1998. A double blind randomized comparison of oral trimeprazine-methadone and ketamine-midazolam for sedation of pediatric dental patients for oral surgical procedures. *AnesthProg.* winter; 45(1):3-11.
- Schmitt M., Nazif M. M., McKee K. C., Zullo T., Venkataramanan R., Burckart G., 1994. Pharmacokinetics and local response to submucosal meperidine compared with other routes of administration. *Pediatr Dent.*; 16:1902.
- Shah A., Mosdossy G., McLeod S., Lehnhardt K. A., 2011. blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *May*; 57(5):425-33.
- Sheroan M. M., Dilley D. C., Lucas W. J., Vann W. F., 2006. A prospective study of 2 sedation regimens in children: Chloral hydrate, meperidine, and hydroxyzine versus midazolam, meperidine, and hydroxyzine. *AnesthProg.*; 53:83-90.
- Song Y. U., Webb M. D., 2003 Comparison of the effect of orally versus submucosally administered meperidine on the behavior of pediatric dental patients: A retrospective study. *AnesthProg.*; 50:12933.
- Veerkamp J. S., Porcelijn T., Gruythuysen R. J., 1997. Intravenous sedation for outpatient treatment of child dental patients: an exploratory study. *Jan-Feb*; 64(1):48-54.
- Watcha M. F., Galinkin J., Fazi L.M., Rose J.B., 1999. Bispectral index (BIS) EEG monitoring in children [abstract A-1266]. Presented at: 1999 American Society of Anesthesiology Meeting; October 13; Dallas, TX.
- Watcha M. F., Fazi L.M., Galinkin J.L., Rose J.B., Chiavacci R.M., 2000. Comparison of bispectral index (BIS) EEG monitoring in children below 2 years age and older children [abstract A-1300]. Presented at: 2000 American Society of Anesthesiology Meeting; October 17; San Francisco, CA.
- Weinstein P., Domoto P. K., Getz T., 1981. Difficult children: the practical experience of 145 private practitioners. *Ped Dent* 1981; 3:303-305.
- Yasny J. S., Asgari A., 2008. Considerations for the use of enteral sedation in pediatric dentistry. *J Clin Pediatr Dent.*; 32:8593.