A Double Blind Randomized Trial of Ketofol Versus Propofol for Endodontic Treatment of Anxious Pediatric Patients

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***Objective**: To find out the safe and efficient sedative agent for primary molar pulpectomy in uncooperative pediatric patients. **Study Design**: This double blind randomized trial enrolled 40 anxious and healthy 2-6 year olds. All subjects received IV propofol (1-1.5mg/kg) or ketofol (1-1.5 mg/kg propofol with 0.25mg/kg ketamine) as per group assignment after oral midazolam premedication (0.5 mg/kg). Sedation maintenance was done with propofol infusion at 25-75µg/kg/min titrated to a predefined Worse level as per Houpt's sedation rating scale. Additional bolus/es was/were administered in the dosage similar to induction dose in case of inadequate sedation. Primary outcomes were intraoperative and postoperative adverse events. Secondary outcomes were vital signs, success of procedure, operator satisfaction, sedation quality, treatment time, recovery time and total propofol dose. **Results**: Significantly greater incidence of respiratory depression was reported for ketofol group (11/20; 55%) when compared to propofol group (3/20; 15%) ($p = 0.008$). Desaturation was the most common adverse respiratory event with significantly greater incidence in ketofol group (9/20; 45%) when compared to propofol only group (3/20; 15%) ($p = 0.033$). No significant differences regarding secondary outcomes were reported in two groups. **Conclusion**: Both the regimen exhibited similar sedation profile while propofol alone emerged as a safer option.*

***Keywords**: Anxiety, Behavior management, Sedation, Propofol, Ketamine, Ketofol*

INTRODUCTION

Fear of dental treatment is ubiquitous[1] and more pronounced in pediatric patients due to emotional immaturity till almost 6 years of age. A tantrum throwing child who screams at top of his voice and refuses to communicate renders the most generous attempts towards behavior management unsuccessful. Worst becomes the scenario when there is an urgent need for dental treatment as in case of an abscessed tooth. Under such circumstances, the pediatric dentist has to resort to pharmacotherapeutic means of behavior managment such as sedation.

Use of inhalation sedation using nitrous oxide has been successfully reported in dentistry.[2-4] However, an associated limitation of nitrous oxide sedation is the requirement of a certain degree of cooperation for mask acceptance, thus restricting its use in potentially uncooperative children and in children <6 years of age.

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A number of other agents have been tried as sedatives for pediatric dental patients such as chloral hydrate,[5-10] meperidine,[8,9,11] hydroxyzine,[6,8] promethazine,[7,9] ketamine,[12,13] propofol[14-16] and midazolam[13,16,17] etc., each having its own advantages and limitations. Out of these propofol is a popular sedative despite its potential for respiratory depression and hypotension.[18] Preliminary research suggests that adding ketamine to propofol might enhance hemodynamic stability, decrease respiratory depression, and stabilizes respiratory drive.[19,20] Few trials in non-dental setting have suggested that use of drug combination of ketamine and propofol named as ketofol is safe and effective for procedural sedation in adult and pediatric population.[19,20] But, no study has been reported till date on use of ketofol in pediatric population undergoing invasive dental procedures. Keeping this in mind the present study was planned in pediatric dentistry department of a tertiary care teaching hospital to compare propofol with ketofol for carrying out endodontic treatment of primary molars in young and anxious children 2-6 years of age.

Our primary outcome was to compare incidence of intraoperative and postoperative complications in propofol versus ketofol. Secondary objectives were to compare vital signs such as heart rate, non-invasive blood pressure (NIBP), respiratory rate, SpO_2; sedation quality, operator satisfaction, parental satisfaction, induction time, treatment time, recovery time and total propofol dose.

MATERIAL AND METHOD

Study Design and Setting

This double blind randomized trial was conducted in pediatric dentistry department of a tertiary care teaching hospital [PGIMER, Chandigarh, India]. The study was approved by University ethical committee review board. The study was conducted from August, 2009 to December, 2011.

Table 1. Modified Post-anesthesia Discharge Scoring System

S.No.	VARIABLE	SCORE
I	**Sensorium**	
	Alert/awake/oriented	2
	Responding to stimuli	1
	Unresponsive	0
II	Motor activity	
	Moves limbs purposefully	2
	Non-purposeful movements	1
	Not moving	0
III	Respiration and oxygenation	
	Normal maintaining SpO2 ≥95%	2
	Tachypnoea but good cough reflex, SpO2≥90% with oxygen	1
	Dyspnea/stridor/chest retraction/weak cough, SpO2≤90% with symbols	0
IV	Postoperative vomiting	
	No vomiting	2
	One or two episodes of vomiting	1
	Severe vomiting (more than 3 episodes of vomiting)	0

Total score = 8

Selection of Participants

A total of 40 children (Figure 1) in the age range of 2-6 years, requiring pulpectomy in at least one carious primary molar and showing anxiety and fear towards dental treatment such as a Venham's score[21] of ≥4 as assessed by first author (NM) during visit to OPD were included in the present study. Only children belonging to physical status ASA (American Society of Anesthesia) I were included. Children with history of previous exposure to general anesthesia or sedation, mental retardation or learning disabilities, obstructed nasal passages, raised intracranial or intraocular pressure, allergy to soya milk or egg, etc. were excluded from this trial.

Children with history of upper respiratory tract infection (URTI) were included only after a time span of ≥4 weeks (after complete resolution of symptoms) has elapsed.

Randomization

A random sequence was generated using the block randomization method. A total of 5 blocks with eight patients in each block were made. The decision to allot the child to either of two groups was based upon randomly choosing a sealed envelope containing details of sedative agent to be administered. The sealed envelopes were prepared beforehand by an investigator [AG] not further involved in outcome assessment in this study.

Interventions

All subjects were premedicated with oral midazolam 0.5mg/kg (Mezolam® Neon, India; 2mg/mL) twenty minutes prior to venous cannulation. Drugs were then administered as *per* group assigned. Subjects in group A (n = 20) received 0.25 mg/kg IV ketamine (Ketalar® Parke Davis, India; 10mg/mL) and 1 mg/kg IV propofol (Diprivan® Astra Zeneca Pharmaceuticals; 10mg/mL) as bolus dose mixed with 2% of 1 ml lignocaine followed by 25-75 µg/kg/min of propofol infusion. Subjects in group B (n = 20) received 1-1.5mg/kg IV bolus of propofol mixed with 2% of 1 ml lignocaine followed by 25-75 µg/kg/min of propofol infusion. The infusion of drugs was titrated to achieve a Houpt's sedation rating score[22] of ≥4 for overall behavior. In case, the sedation level of the child was insufficient to reach this effect, additional 1-1.5mg/kg IV bolus of propofol along with 2% of 1 ml lignocaine or 1-1.5mg/kg IV bolus of propofol plus 0.25 mg/kg IV bolus of ketamine along with 2% of 1 ml lignocaine were administered. All subjects were supplemented by intravenous normal saline at rate of 2mL/kg/hr throughout the procedure.

Blinding

Corneal taping was used to mask the typical nystagmus observed with ketamine. The induction bolus as well as additional boluses were administered by syringes covered with opaque paper to mask the obvious differences between color of ketamine and propofol.

Methods of Record Keeping and Measurements

The data for each patient was entered on pre-printed proformas which included details of drugs administered (total dose and additional boluses), vital signs such as heart rate, NIBP (Non-invasive blood pressure), respiratory rate, SpO_2; Houpt's sedation scores at various predecided time points of measurements, success of procedure, parental satisfaction, induction time, treatment time, recovery time, any complications and their management.

Vital signs were recorded every 5 minutes using monitor (GE Datex Ohmeda S/5 Aespire Anesthesia Machine, United Kingdom). Houpt's sedation scores were recorded at various procedural steps such as baseline, venepuncture, separation from parents, administration of local anesthesia, application of rubber dam, preparation of access cavity, extirpation of pulp, removal of rubber dam and exit from operatory to recovery room.

Proceedings of dental procedure were recorded as 1 = Smooth and completed, 2 = Completed with interruptions and 3 = Incomplete. Parental satisfaction was recorded on a Likert type scale ranging from 1 to 5 i.e. 1= excellent, 2 = good, 3 = fair, 4 = satisfactory and 5 = poor. The induction time was defined as time from intravenous injection of induction bolus till the sedation level was sufficient for the procedure to be started. Time period from injecting local anesthesia to removal of rubber dam was defined as treatment time. Post-operative recovery was assessed by applying modified post anesthesia discharge scoring system (Table 1). Patient assessment in recovery was done every 5 minutes.

Outcome Measures

Primary outcome measure in this trial was incidence of intraoperative and postoperative complications. A pulse rate of <60 was considered to be bradycardia and >140 as tachycardia. Respiratory depression was defined as occurrence of one of the following parameters:

- *Desaturation*: SpO2 less than 94%
- *Apnea*: Any event of cessation of breathing with no visible respiratory effort for greater than 15 seconds
- Any other event requiring airway manipulation i.e. stridor, coughing, laryngospasm.

Secondary outcome measures in this trial consisted of quality of sedation as assessed by Houpt's sedation rating scale;[22] vital signs (heart rate, NIBP, respiratory rate, SpO_2), proceedings of dental procedure, parental satisfaction, induction time, treatment time, recovery time, total propofol dose, additional drug boluses required.

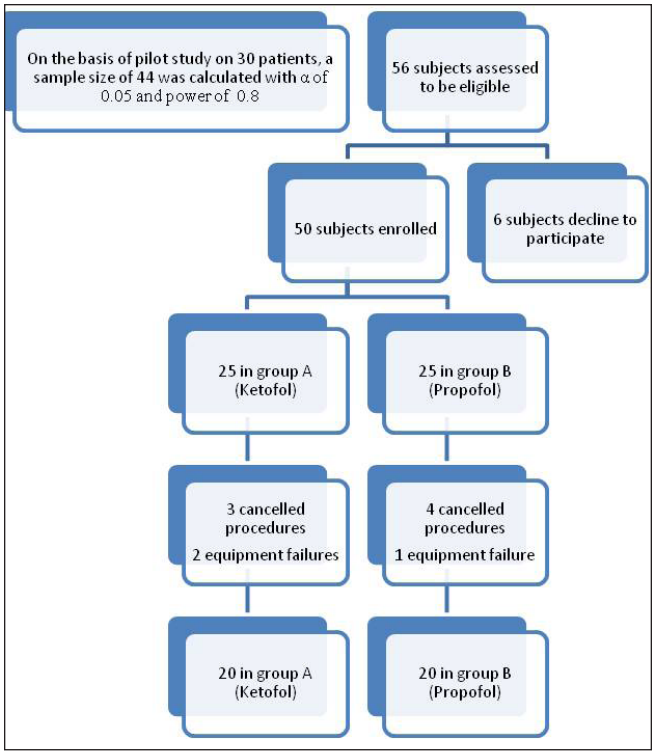

Figure 1. Flow of participants during trial

Statistical Analysis

For variables such as heart rate, NIBP, respiratory rate, oxygen saturation following a normal distribution as shown by results of Kolmogorov-Smirnov test, paired t-test was used for intergroup comparison. For quantitative data following non-normal distribution i.e. Houpt's sedation scores, parental satisfaction scores, induction time, procedure time, recovery time and propofol dose (mg/kg) Mann-Whitney U test was applied for intergroup comparison. For qualitative variables Venham's anxiety score, proceedings of procedure, requirement for additional drug boluses; Chi-square test was used for intergroup comparison. Significance level was taken at $p \leq 0.05$.

RESULTS

Figure 1 shows flow of participants during the trial. Baseline demographic characteristics were similar in both the groups (Table 2). The difference in baseline anxiety scores as per Venham's anxiety rating scale was statistically significant amongst the two groups. But, this difference was not clinically significant as children with Venham's anxiety score of either 4 or 5 are not amenable to routine behavior management techniques.

For primary outcome such as incidence of complication rate, difference in two study groups was highly significant (Table 3, p=0.008) with ketofol group showing significantly more episodes of respiratory depression. Regarding individual measures of intra-operative complication significantly more episodes of desaturation occurred in ketofol group (Table 3, p=0.033).

Regarding secondary outcome, the quality of sedation was similar in two study groups as depicted by similar Houpt's sedation rating score (Figure 2) at various time points of measurements.

At 0 minute, all vital signs i.e. heart rate, NIBP, respiratory rate and oxygen saturation were comparable between the two groups. At 5 min, heart rate increased as compared to baseline in ketofol group while it remained stable in propofol group (Figure 3a). The difference in heart rate between two groups was significant at 15, 20, 25 and 30 minute (p = 0.016, 0.007, 0.005 and 0.002 respectively) of observation period. No significant differences were reported between the two groups regarding any other vital sign parameter (Figure 3 b, 3c, 3d).

In the ketofol group, endodontic procedure could not be completed in 2 patients while in propofol group the procedure was successfully completed in all the patients (Table 4, p =0.287). Parental satisfaction was not statistically different amongst the two study groups (Table 4, p =0.287). Statistically insignificant differences between the two study groups were reported with respect to induction time (Table 4, p =0.681), procedure duration (Table 4, p =0.473) and recovery time (Table 4, p =0.682). Mean propofol dose administered and requirement for additional drug boluses was lesser in ketofol group when compared to propofol only group, however, this difference was statistically insignificant (Table 4, p =0.350).

LIMITATION

Maintaining blinding with ketamine was challenging even though we used corneal taping to mask the typical nystagmus observed with ketamine. No attempts were made to test the blinding efficacy and this was the principal limitation of our trial.

Most of our study outcomes are objective and thus should remain reliable, regardless; however, our parental satisfaction scoring criteria is subjective. This may have been influenced by operator/outcome assessor because of openness of scoring criteria.

Table 2. Baseline characteristics of ketamine/propofol and propofol-alone groups.

Group characteristics	Group A (Ketofol) n = 20	Group B (Propofol) n = 20	p value
Age in months	46.60 ± 11.320	44.65 ± 16.204	0.662†
Male (%)	60	50	> 0.05≠
Weight in kgs	14.50 ± 3.777	14.50 ± 4.947	0.901†
Anxiety scores as per Venham's anxiety rating scale	4.60 ± 0.503	4.94 ± 0.224	0.007ᵞ**

† Calculated on the basis of paired t-test.; ᵞ Calculated by applying Mann-whitney U test; ≠ Calculated on the basis of Chi square test
** denotes highly significant p value

Table 3. Primary outcome variables in two study groups

Primary outcome variable n (%)	Group A (Ketofol) n = 20	Group B (Propofol) n = 20	p value†
Apnoea	1 (5)	2 (10)	0.548
Desaturation	9 (45)	3 (15)	0.033*
Stridor	2 (10)	1 (5)	0.548
Coughing	3 (15)	1 (5)	0.292
Laryngospasm	1 (5)	0 (0)	0.311
Total (complication of any kind)	11 (55)	3 (15)	0.008**

†Calculated by using Chi Square test; *denotes significant p value,
** denotes highly significant p value

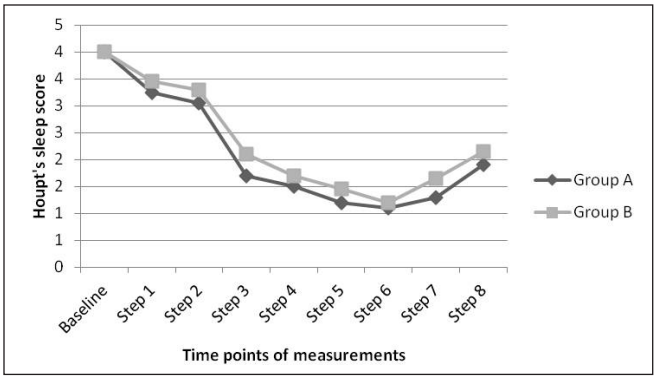

Figure 2a. Houpt's sleep score in two study groups at various steps of treatment*

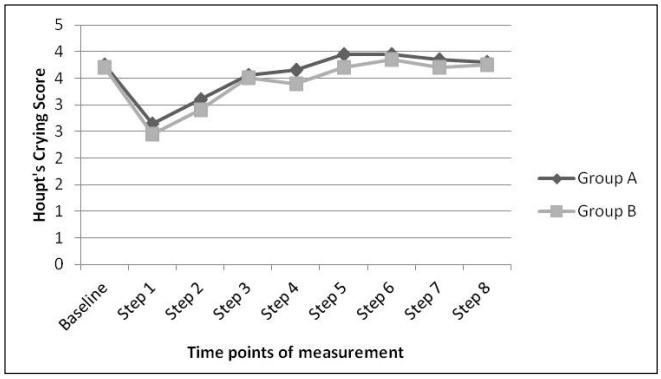

Figure 2b. Houpt's crying score in two study groups at various steps of treatment*

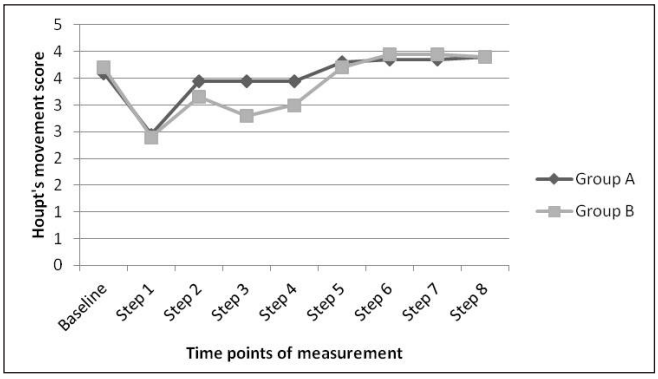

Figure 2c. Houpt's movement score in two study groups at various steps of treatment*

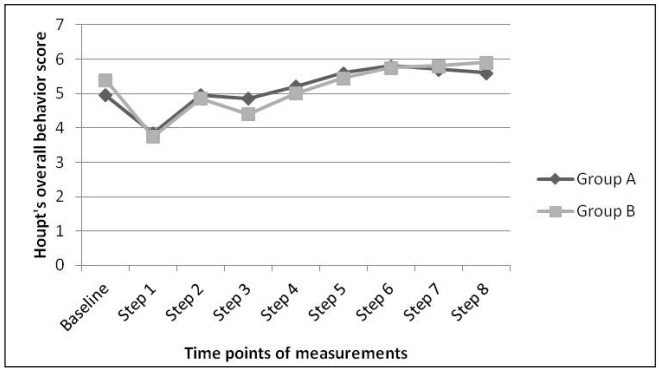

Figure 2d. Houpt's overall behavior score in two study groups at various steps of treatment*

*Various steps of treatment: Baseline, Step 1: Venepuncture, Step 2: Separation from parents, Step 3: Administration of local anesthesia, Step 4: Application of rubberdam, Step 5: Preparation of access cavity, Step 6: Extirpation of pulp, Step 7: Removal of rubber dam and Step 8: Exit from operatory to recovery room

DISCUSSION

To the best of our knowledge, this is the first double blind randomized controlled trial of ketamine/propofol (ketofol) versus propofol alone in the pediatric dentistry setting. Although both of the sedation regimens provided similar results regarding secondary outcomes, propofol emerged as a safer option when compared to ketofol as observed after analyzing results for primary outcome.

Tomatir *et al*,[19] Singh *et al*,[23] David and Shipp[24] and various other authors found greater incidence of respiratory complications in propofol group when compared to ketofol group. While in present study a reverse trend was observed with ketofol.

A total of 5/6 desaturation events observed with this combination were accompanied by excessive salivary secretions. Stimulation of salivary secretions is a well known side effect of Ketamine administration and is of concern because of associated airway complications.[25,26] Also, in the present study the zone of operation was oral cavity and this could have augmented the stimulatory effect of ketamine on salivary secretions. Such an implication of salivary stimulation in greater airway adverse effects by ketofol has been supported by findings of Daabiss *et al* [26] Since this is first study of its kind to test the safety and efficacy of propofol vs ketofol in dental setting, direct comparisons could not be drawn.

A lower dose of ketamine i.e. 0.25 mg/kg was administered to decrease the salivary stimulation which could have otherwise choked the patients resulting in desaturation. Though co-administered anticholinergic agents have been traditionally recommended during ketamine sedation in children with the intent of minimizing oral secretions and thus, presumably, airway adverse events. Their efficacy in this role is controversial. A recent large observational meta-analysis by Green SM *et al* [27] found that coadministered anticholinergics did not reduce airway adverse events, instead they led to tachycardia. Thus, instead of relying on anticholinergics to reduce salivary flow, we used a lower dose 0.25 mg/kg of ketamine while glycopyrollate 0.1µg/kg was administered only in case where despite low dose of ketamine increased secretions were noted.

An increase in heart rate in ketofol group was observed in the present study, which is in agreement with other studies as ketamine's known sympathomimetic effects have been observed at dosages as low as 0.3 mg/kg.[28] The stable vital parameters i.e. no incidence of hypotension or bradycardia observed in propofol group could be due to smaller dose and use of infusion method of drug titration. It is recognized that slower infusion of the same bolus dose results in lower peak serum concentrations and reduced target organ effects.[29]

The results of the present study are not in agreement with studies done by Tosun *et al* [30] and Singh *et al* [23] where ketofol group was judged to be a better sedative, as in the present study, comparable sedation has been found in both groups. This could be because of the reason that in our study sedation end points were predefined. A goal sedation of Houpt's score of ≥4 for overall behavior was targeted. The study protocol allowed titration of drug infusion between 25-75 µg/kg/min. However, if need arose, rescue boluses were administered as per group for completion of procedure without interruptions.

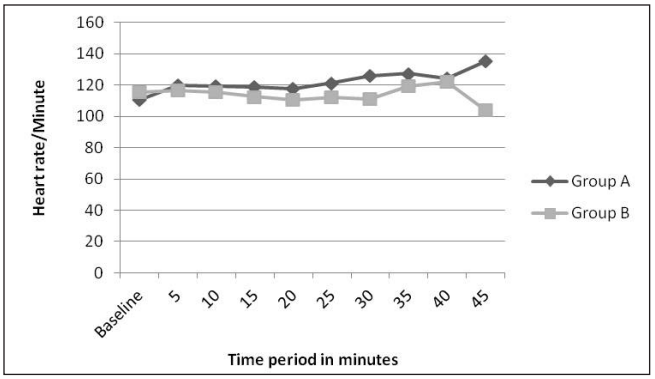

Figure 3a. Variation in heart rate during treatment progression in two study groups

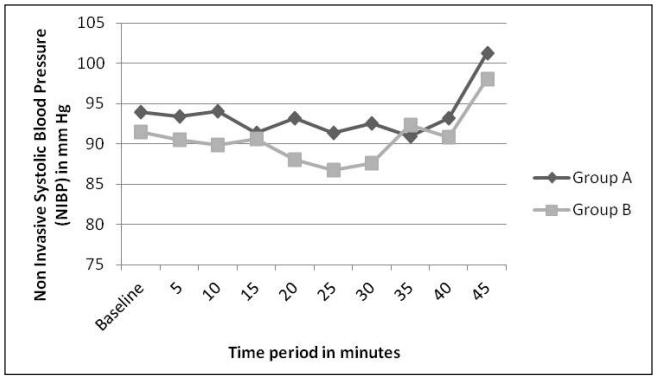

Figure 3b. Variation in systolic non-invasive blood pressure during treatment progression in two study groups

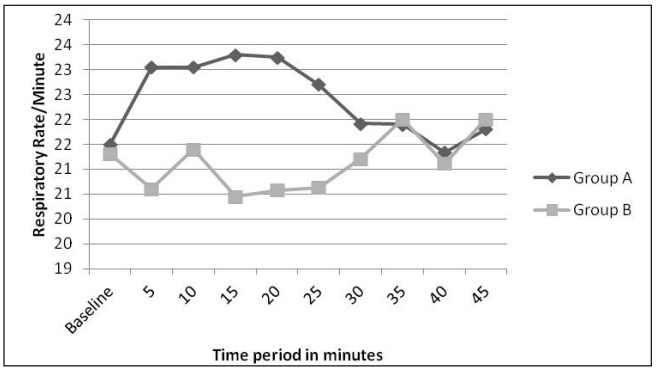

Figure 3c. Variation in respiratory rate during treatment progression in two study groups

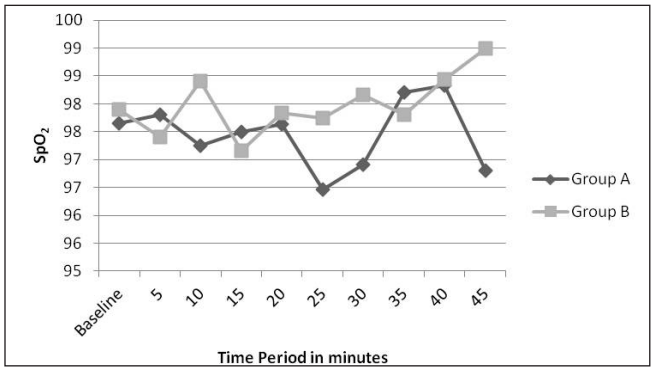

Figure 3d. Variation in SpO2 during treatment progression in two study groups

Although investigators have recently suggested that bispectral index (BIS) may provide an objective, clinically useful tool to assess sedation depth in children,[31-33] we did not use this tool as a measure of sedation depth. Several studies suggest that BIS may be less reliable in detecting sedation depth as BIS may be drug dependent.[34-37] Ketamine has been shown to similarly depress level of consciousness without lowering BIS values.[35-37] In fact, some studies have found a paradoxical increase in BIS despite deepening levels of hypnosis after ketamine administration in patients anesthetized with sevoflurane or propofol.[35] This effect may reflect a desynchronization of the EEG signal from the dissociative action of ketamine.[37] For these reasons we did not use BIS in our study, rather we relied on clinical scoring system i.e. Houpt sedation scoring criteria to monitor sedation.

Because of the fact that propofol acts by cortical depression and ketamine is a dissociative sedative acting on subcortical level, a synergistic sedative effect should result on combination of propofol and ketamine. This theoretical assumption anticipates faster induction and delayed recovery. Although statistically significant differences could not be observed in two groups regarding induction time, procedure time and recovery time; a trend towards faster induction and delayed recovery could be appreciated in ketofol group.

The mean procedure time in propofol and ketofol group was 34.20 minutes and 38.40 minutes respectively. This time duration is much lower than the time usually employed for endodontic treatment of primary molar in conjunction with routine behavior management techniques in clinic. This signifies effect of sedative regimen used in present study to ease carrying out an endodontic procedure smoothly.

Table 4. Secondary outcome variables in two study groups

Secondary outcome variable	Group A (Ketofol) n = 20	Group B (Propofol) n = 20	p value
Total Propofol dose in mgs (mean ± SD)	42.34 ± 22.50	50.29 ± 30.066	0.350≠
Number of patients who needed additional drug bolus; n (%)	5 (25)	8 (40)	0.311†
Parental satisfaction (% with score 1 or 2); n (%)	18 (90)	20 (100)	0.287†
Incomplete procedures; n (%)	2 (10)	0 (0)	0.287†
Mean VAS scores (mean ± SD)	2.25 ± 1.372	1.75 ± 1.164	0.222γ
Induction time in minutes (mean ± SD)	3.95 ± 2.781	4.30 ± 2.557	0.681γ
Procedure time in minutes (mean ± SD)	36.05 ± 14.724	33.40 ± 7.081	0.473γ
Recovery time in minutes (mean ± SD)	24.50 ± 25.542	22.00 ± 9.090	0.682γ

≠Calculated by using Mann-Whitney U test; †Calculated by using Chi Square test;

γ Calculated by applying Mann-whitney U test

CONCLUSIONS

Propofol is superior to ketofol in terms of safety as it showed fewer adverse effects than the latter as observed in the present study. Ketamine is to be chosen with caution while operating in proximity to airway i.e. oral cavity. Treatment under propofol sedation is a time saving endeavor as endodontic treatment in primary molar was completed in almost half of the time duration than usually required in non-sedative clinical setting employing routine behavior management techniques. However, Propofol should be used only in presence of a dedicated sedation staff and vital sign monitor to ensure constant intraoperative and postoperative monitoring because of its potential to cause respiratory depression.

REFERENCES

1. Weinstein P, Nathan JE. The challenges of fearful and phobic children. *Dent Clin North Am 32*: 667-92, 1988.
2. Hallonsten AL. Nitrous oxide oxygen sedation in dentistry. *Swed Dent J suppl 14:* 9-10, 1982.
3. Veerkamp JSJ, Van Amerongen WE, Hoogstrten J, Groen HJ. Dental treatment of fearful children using nitrous oxide. Part I: Treatment Times. *J Dent Child 6*: 453-7, 1991.
4. Veerkamp JSJ, Gruthuysen RJM, Van Amerongen WE, Hoogstrten J. Dental treatment of fearful children using nitrous oxide. Part III : Anxiety during sequential visits. *J Dent Child 3*: 175-82, 1993.
5. Houpt MI, Sheskin RB, Koenigsberg SR, Desjardins PJ, Shey Z. Assessing chloral hydrate dosage for young children. *J Dent Child 52*: 364-369, 1985.
6. Gladney, Stanley RT, Hendricks SE. Anxiolytic activity of chloral hydrate and hydroxyzine. *Ped Dent 16*: 183-7, 1994.
7. Davila JM, Herman AE, Proskin HM, Vitale D. Comparison of sedative effectiveness of two pharmacological regimens. *J Dent Child 61*:276-281, 1994.
8. Nathan JE, West MS. Comparison of chloral hydrate- hydroxizine with and without meperidine for management of difficult pediatric patients. *J Dent Child 54*: 437-443, 1987.
9. Sams DR, Thorton JB, Wright JM. The assessment of two oral sedation drug regimens in pediatric dental patients. *J Dent Child 59*: 306-312, 1992.
10. Littman RS, Kotra JA, Verga RA, Berkowitz RJ, Ward DS. Chloral hydrate sedation. The additive sedative and respiratory depressant effect of nitrous oxide. *Anesth Analg 86*: 724-728, 1998.
11. Haney KL, McWhorter AG, Scale NS. An assessment of success of meperidine and promethazine sedation in medically compromised children. *J Dent Child 60*: s 288-295, 1993.
12. Bui T, Redden JR, Murphy S. A comparison study between ketamine and ketamine-promethazine combination for oral sedation in pediatric dental patients. *Anesth Prog 49:*14-18, 2002.
13. Roelofse AJ, Joubert VDJJ, Roelofse RGP. A Double-Blind Randomized Comparison of Midazolam Alone and Midazolam Combined With Ketamine for Sedation of Pediatric Dental Patients. *J Oral Maxillofac Surg 54*: 238-844, 1996.
14. Arya VS, Damle SG. Comparative evaluation of Midazolam and Propofol as intravenous sedative agents in the management of unco-operative children. *J Indian Soc Pedod Prev Dent 20*:6-8, 2002.
15. Hosey TM, Makin A, Jones MR, Gilchris F, Carruthers M. Propofol intravenous conscious sedation for anxious children in a specialist paediatric dentistry unit. *Int J Paediatr Dent 14*: 2–8, 2004.
16. Rai K, Hegde M A, Goel K. Sedation in uncooperative children undergoing dental procedures: a comparative evaluation of midazolam, propofol and ketamine. *J Clin Pediatr Dent 32*:1-4, 2007.
17. Kapur A, Chawla SH, Goyal A, Gauba K, Bhardwaj N. Efficacy and acceptabilty of oral-transmucosal midazolam as a conscious sedation agent in pre-school children. *J Indian Soc Pedod Prev Dent 22*:109-13, 2004
18. Bryson MH , Fulton RB, Faulds D. Propofol an update of its use in anesthesia and conscious sedation. *Drugs 50*:513-59, 1995.
19. Tomatir E, Atalay H, Gurses E, Erbay H, Bozkurt P. Effects of low dose ketamine before induction on propofol anesthesia for pediatric magnetic resonance imaging. *Paediatr Anaesth 14*:845-850, 2004.
20. Akin A, Esmaoglu A, Tosun Z, Gulcu N, Aydogan H, Boyaci A. Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. *Int J Pediatr Otorhinolaryngol 69*:1541-1545, 2005.
21. Venham L. The effect of mother's presence on child's response to dental treatment. *J Dent Child 46*:219-225, 1979.
22. Houpt M. Project USAP the use of sedative agents in dentistry. *Pediatr Dent 15*: 36-40, 1993.
23. Singh R, Batra KY, Bhari, Panda BN. Comparison of propofol versus propofol-ketamine combination for sedation during spinal anesthesia in children: randomized clinical trial of efficacy and safety. *Pediatr Anesth 20:* 439–444, 2010.
24. David H, Shipp J. A randomized controlled trial of Ketamine/Propofol versus Propofol alone for emergency department procedural sedation. *Ann Emer Med 57*: 435-42, 2011.
25. Aroni F, Iacovidou N, Dontas I, Pourzitaki C and Xanthos T. Pharmacological Aspects and Potential New Clinical Applications of Ketamine: Reevaluation of an Old Drug. *J Clin Pharmacol 49*: 957-63, 2009.
26. Daabiss M, Elsherbiny M, Al Otibi R. Assessment of different concentrations of Ketofol in procedural sedation. *Br J Med Pr 552*: 27-31, 2009.
27. Green MS, Roback GM, Krauss B. Anticholinergics and Ketamine Sedation in Children: A Secondary Analysis of Atropine Versus Glycopyrrolate. *Acad Emerg Med 17*:157–162, 2010.
28. Messenger WD, Murray EH, Dungey EP, Sivilotti ALM. Subdissociative-dose Ketamine versus Fentanyl for Analgesia during Propofol Procedural Sedation: A Randomized Clinical Trial. *Acad Emerg Med 15*:877–886, 2008.
29. Struys MM, Coppens MJ, De Neve N, Mortier EP, Doufas AG, Van Bocxlaer JF, Shafer SL. Influence of administration rate on propofol plasma-effect site equilibration. *Anesthesiology 107*:386–96, 2007.
30. Tosun Z, Aksu R, Guler G, Esmaoglu A, Akin A, Aslan E, Boyaci A. Propofol-ketamine vs propofol-fentanyl for sedation during pediatric upper gastrointestinal endoscopy. *Pediatric Anesthesia 17*: 983–988, 2007.
31. Berkenbosch JW, Fichter CR, Tobias JD. The correlation of the bispectral index monitor with clinical sedation scores during mechanical ventilation in the pediatric intensive care unit. *Anesth Analg 94*:506–511, 2002.
32. Powers KS, Nazarian EB, Tapyrik SA, Kohli MS, Yin H, van der Jagt WE, Sullivan SJ, Rubenstein SJ. Bispectral index as a guide for titration of propofol during procedural sedation among children. *Pediatrics 115*:1666–1674, 2005.
33. Grindstaff RJ, Tobias JD. Applications of bispectral index monitoring in the pediatric intensive care unit. *J Intensive Care Med 19*:111–116, 2004.
34. Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth Analg 101*:765–773, 2005.
35. Sakai T, Singh H, Mi WD, Kudo T, Matsuki A. The effect of ketamine on clinical endpoints of hypnosis and EEG variables during propofol infusion. *Acta Anaesthesiol Scand 43*: 212–216, 1999;
36. Vereecke HE, Struys MM, Mortier EP. A comparison of bispectral index and ARX-derived auditory evoked potential index in measuring the clinical interaction between ketamine and propofol anaesthesia. *Anaesthesia 58*: 957–961, 2003.
37. Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. *Br J Anaesth 94*:336–340, 2005.