ORIGINAL ARTICLE

To Compare the Efficacy of Two Intravenous Combinations of Drugs Ketamine–Propofol vs Ketamine–Dexmedetomidine for Sedation in Children Undergoing Dental Treatment

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Abstract

Objective: To compare the efficacy of two intravenous combinations of drugs ketamine–propofol (KP) vs ketamine–dexmedetomidine (KD) for sedation in children undergoing dental treatment.

Study design: Thirty patients were selected, evaluated according to the predetermined criteria and divided in equal numbers of 15 amongst 2 groups KP and KD.

Materials and methods: Informed consent was taken, nil per oral (NPO) guidelines were followed and the study drug was administered. Dental procedure was performed. Heart rate (HR), blood pressure (BP) and oxygen saturation (SPO_2) were monitored continuously throughout the procedure. The modified Ramsay sedation (MRS) score was recorded along with Houpt sedation score. Recovery status was accessed by modified Aldrete's recovery scale.

Statistical analysis: Student t test was used for comparing HR, BP and SPO_2. Chi-square test was used to compare MRS, Houpt sedation score and modified Aldrete's recovery scale amongst the two groups KP and KD.

Results: The sedation achieved with both the groups was adequate. Both the drugs produce adequate hemodynamic stability.

Conclusion: Ketamine–dexmedetomidine has a better efficacy over the other group, ketamine–propofol.

Keywords: Dental treatment, Dexmedetomidine, Intravenous sedation, Ketamine, Propofol.

International Journal of Clinical Pediatric Dentistry (2020): 10.5005/jp-journals-10005-1826

Introduction

Providing dental care without causing any psychological impact on the child is a herculean task in the field of pediatric dentistry. Any uncooperative behavior on the part of the child makes it difficult to provide safe and effective dental treatment. Conventional behavior management techniques should help in providing a complete and effective dental care which eventually will instill a positive mental attitude in the child. On the contrary, conventional methods are not always possible.[1] The most ideal solution in these cases would be to switch over to pharmacological behavior management techniques, wherein the dentist will be able to provide effective and safe dental treatment.[2] Hence, in such likely scenarios, conscious sedation or premeditation with pharmacologic agents should be opted.

For sedation, various medications are administered either as a single drug or in combination with another drug to produce synergistic action. Different routes of administration can be used, and they include oral and intravenous routes. The results obtained have been variable with respect to efficacy and safety. No single drug has been identified as an ideal sedative agent. Therefore, no drug has achieved a universal acceptance. Similar adverse effects have been observed with administration of both single drug and combinations of drugs.[3]

Popular drugs that are used in dental sedation are nitrous oxide, midazolam, ketamine, propofol, dexmedetomidine, etc.

Ketamine, a phencyclidine derivative, is available as ketamine hydrochloride which is a mixture of two isomers S and R. It is an excellent analgesic and produces a characteristic state of "dissociative anesthesia". Ketamine has a wide margin of safety with the protective reflexes of the airway usually being maintained.[4,5] Use of ketamine is limited by development of hallucinations in the postoperative period, although it is much less common in children. Subanesthetic doses (0.5–1.0 mg/kg) of ketamine provide sedation with analgesia.

Propofol, 2.6-diisopropylphenol, is an intravenous anesthetic agent that is used for induction of anesthesia and procedural sedation. Propofol, in the dose 2 mg/kg intravenous dose, induces general anesthesia, whilesub anesthetic dose (25–50 µg/kg/minute) produces sedation. It also has antiemetic and antipruritic properties. The recovery associated with propofol is rapid and of high quality.[6] Interestingly, physical mixture of ketamine and propofol, often

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How to cite this article: Joshi AB, Shankaranarayan UR, Hegde A, *et al.* To Compare the Efficacy of Two Intravenous Combinations of Drugs Ketamine–Propofol vs Ketamine–Dexmedetomidine for Sedation in Children Undergoing Dental Treatment. Int J Clin Pediatr Dent 2020;13(5):529–535.

Source of support: Nil

Conflict of interest: None

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called "ketofol", has also been found to be effective in providing sedation. Here, both the drugs are used in smaller doses.[7]

Dexmedetomidine is a newer centrally acting α2 agonist that provides sedation and analgesia without significant respiratory depression. The sedation produced by this drug mimics some aspects of natural sleep. However, dexmedetomidine does depress the cardiovascular system, producing bradycardia and hypotension. Paradoxically, hypertension can also be seen in some patients. It has been used extensively for sedation in all age-groups including children with excellent safety profile.[8] Ketamine and dexmedetomidine act synergistically to provide excellent sedation with minimal side effects.[9]

In this study, we compared two different combinations, i.e., ketamine with propofol and ketamine with dexmedetomidine, for their efficacy in children undergoing dental treatment under sedation.

Aim and Objective of the Study

To compare the efficacy of two intravenous combination of drug Ketamine-Propofol (KP) vs Ketamine-Dexmedetomidine (KD) for sedation in children undergoing dental treatment.

Materials and Methods

Thirty children in the age-group 4–8 years, visiting the outpatient department of Pedodontics and Preventive dentistry, were included in this study. Healthy children with dental problems, anxious, and apprehensive were enrolled in the study, irrespective of their gender and socioeconomic status. Children were distributed equally between the two groups randomly

- Group KP: ketamine with propofol
- Group KD: ketamine with dexmedetomidine

The American Society for Anesthesiologists[10] status of the children was determined and a global behavior rating was also assigned using Frankl's behavior rating scale.[11]

Inclusion Criteria

- Children exhibiting Frankl's behavior rating score II or III.
- Children requiring any comprehensive dental treatment.
  - Restorations
  - Extractions
  - Pulp therapy (with or without LA)
- Children with ASA I or II physical status.

Exclusion Criteria

- Children requiring major surgical procedures.
- Children requiring dental procedures of more than 45 minutes duration.
- Children who are differently abled.

Informed consent for a course of dental treatment under conscious sedation was obtained from each parent/guardian. The NPO guidelines followed were: (i) no solid for 6 hours before the surgery and (ii) no clear fluids within two hours before surgery. The patients were encouraged to take tender coconut water up to 3 hours before the procedure to improve patient satisfaction and prevent hydration. Vital signs (heart rate, oxygen saturation, and blood pressure) were recorded as follows:

- Before premedication in KM group
- After 15 minutes of premedication in KM group
- Before sedating the patient,
- Every 5 minutes of the procedure
- After the procedure.

Electrocardiogram was continuously monitored in all patients. The sedation scores was recorded based on Modified Ramsay sedation score[12] (Table 1) and sedation score by Houpt et al.[13] (Table 2).

All children were premedicated 30 minutes prior to the procedure with oral midazolam (0.5 mg/kg). For patients of Group

Table 1: Modified Ramsay sedation score[12]

Score	*Characteristics*
1	Awake and alert, minimal or no cognitive impairment
2	Awake but tranquil, purposeful responses to verbal commands at conversation level
3	Appears asleep, purposeful responses to verbal commands at conversation level
4	Asleep, purposeful responses to verbal commands at conversation level but at louder than usual conversation level or requiring light glabellar tap
5	Asleep, sluggish purposeful responses only to verbal commands or strong glabellar tap
6	Asleep, sluggish purposeful responses only to painful stimuli
7	Asleep, reflex withdrawal to painful stimuli only (no purposeful response)
8	Unresponsive to external stimuli, including pain

Table 2: Sedation score by Houpt et al.[13]

Score	*Rating scale*
(A) Sleep	
4	Awake, but responsive
3	Drowsy, disoriented
2	Asleep, easily aroused
1	Asleep, difficult to arouse
(B) Movement	
4	No movement
3	Intermittent movement affecting treatment
2	Continuous movement affecting treatment
1	Violent movement that interrupted or prevented the treatment
(C) Crying	
4	No crying
3	Intermittent crying
2	Continuous crying
1	Hysterical crying
Overall behavior	
6	Excellent, no disruption
5	Very good, limited disruption
4	Good, some difficulty
3	Fair, much difficulty but treatment done
2	Poor, partial treatment done
1	Aborted

KP and KD, eutectic mixture of local anesthetic (EMLA) was applied to the non-dominating hand of the patient by 22-gauge cannula.
Group KP: Received propofol 1 mg/kg and ketamine 1 mg/kg over a period of 2–3 minutes.
Group KD: Received dexmedetomidine 1 µg/kg and ketamine 1 mg/kg over a period of 2–3 minutes.

During the procedure, top-up doses of ketamine were used, 5 mg/dose.

Anesthesiologist was present from the start of the procedure for the delivery of the study drug and monitoring till the recovery of the patient. All patients were administered supplemental oxygen throughout the procedure through a nasal cannula at a flow rate of 3 liter/minute.

Once the patient was adequately sedated, dental treatment was started. Patient is considered adequately sedated when–

- Eyelash reflex is absent
- Jaw is relaxed
- Sedation score of 3 or 4 (Modified Ramsay sedation score)

Any variation in the above points was noted, and child was said to be not adequately or excessively sedated.

Vital signs were monitored on shifting to recovery area and at 5 minute intervals thereafter till the time of discharge. The recovery of each patient was recorded using Modified Aldrete's recovery scale (Table 3).[14] Patients were given clear fluids to drink 3 hours postprocedure. If the patient accepted it without any difficulty, then they were allowed to take semisolid foods. Every patient was monitored by qualified nurse. During this period, vital signs were noted every 15 minutes up to 1 hour. Observation was continued if Aldrete's scale was low. According to this system, a total score of 8 or more was used as criteria for discharge from the dental setup (Table 4).
Criteria for discharge were:

- Stable vital signs (room air oxygen saturation >97%, and heart rate above 80 mm Hg and below 120 mm Hg)
- Airway patency was maintained with satisfactory breathing (respiratory rate >12 minute)
- Adequate hydration.
- Patient was oriented to time and place.
- Ability to sit unaided.
- Ability to ambulate.
- Responsible individual to accompany the child.

All the data were statistically analyzed by Chi-square test and Student-*t* test.

Results

The comparison between the two groups KP and KD was done by statistical analysis using SPSS v1.2 with the help of Chi-square test and Student *t* test. The ketamine–propofol combination was compared with ketamine–dexmedetomidine for changes in heart rate, blood pressure, and oxygen saturation.

Table 3: Modified Aldrete's recovery scale[14]

Score	*Rating scale*
Activity: ability to move voluntarily or on command	
2	4 extremities
1	2 extremities
0	0 extremity
Respiration	
2	Able to breathe deeply and cough freely
1	Dyspnea, shallow or limited breathing
0	Apneic
Circulation	
2	BP ± 20 mm of pre-PSA level
1	BP ± 20—50 mm of pre-PSA level
0	BP ± 50 mm of pre-PSA level
Consciousness	
2	Fully awake
1	Arousal on calling
0	No response
Color	
2	Normal
1	Pale, dusky, blotchy
0	Cyanotic

Table 4: Chi-square test for the modified Ramsay sedation score (MRS)

Crosstab for MRS after the administration of drugs

			Group		
			Ketamine and propofol	*Ketamine and dexmeditomidine*	*Total*
MRS after	3	Count	8	2	10
		% within group	53.3%	13.3%	33.3%
	4	Count	7	7	14
		% within group	46.7%	46.7%	46.7%
	5	Count	0	6	6
		% within group	0.0%	40.0%	20.0%
Total		Count	15	15	30
		% within group	100.0%	100.0%	100.0%

Chi-square tests

	Value	*df*	*Asymp. sig. (2-sided)*
Pearson Chi-square	9.600	2	0.008
N of valid cases	30		

The *p* value was found to be highly significant (<0.001) for heart rate. The heart rate was significantly high in KP group throughout the procedure compared to KD group. The *p* value for systolic blood pressure was <0.001 and for diastolic blood pressure was also <0.001, which suggested the highly significant difference between the two groups KP and KD. The KP group showed higher blood pressure than the other group.

The changes in oxygen saturation between the two groups was insignificant with a *p* value of >0.05. The saturation was maintained above 95% throughout the procedure in both the groups.

The Modified Ramsay sedation score (MRS) was recorded and compared at three different time intervals, immediately after the delivery of drug, after 5 minutes of delivery of drug, and then at the end of the procedure. MRS score between the two groups KP and KD, immediately after the delivery of drug, was similar. At 5 minutes of the delivery of the drug, the difference between the two groups was highly significant with *p* value of <0.001. The quality of sedation was better in KD group. Also, the MRS score at the end of the procedure was similar in both the groups.

Houpt et al. sedation score was also recorded at three time intervals similar to MRS score. The Houpt sedation score has four subcategories: sleep, crying, movement, and overall score. All the categories were assessed at three different time intervals. Houpt score for crying and movement showed no statistically significant difference between the two groups KP and KD, whereas the score for sleep showed statistically significant difference between the two groups KP and KD immediately after the delivery of the drug with the *p* value of 0.007 (Table 5). The children showed better quality of sedation in KD group. Thereafter, there was no difference between the scores after 5 minutes of drug delivery or at the end of the procedure.

The overall Houpt et al. sedation score between the two groups KP and KD, immediately after the delivery of drug, was similar. The *p* value on comparison between the two groups for overall Houpt et al. sedation score immediately after the delivery of drug was insignificant (0.464), after the delivery of the drug was also insignificant with the value of 0.136 but was highly significant at the end of the procedure with a value of <0.001 (Table 6). The graphs represent the comparison between the groups.

Table 5: Chi-square test for the Houpt sedation score for crying

Crosstab for Houpt sedation score for crying immediately after the delivery of drugs

			Group		
			Ketamine and propofol	*Ketamine and dexmeditomidine*	*Total*
Houpt Sleep 1	2	Count	1	9	10
		% within group	6.7%	60.0%	33.3%
	3	Count	13	6	19
		% within group	86.7%	40.0%	63.3%
	4	Count	1	0	1
		% within group	6.7%	0.0%	3.3%
Total		Count	15	15	30
		% within group	100.0%	100.0%	100.0%

Chi-square tests

	Value	*df*	*Asymp. sig. (2-sided)*
Pearson Chi-square	9.979[a]	2	0.007
N of valid cases	30		

[a]2 cells (33.3%) have expected count less than 5. The minimum expected count is 0.50

Table 6: Chi-square test for the Houpt overall sedation

Crosstab for Houpt overall sedation score at the end of the procedure

			Group		
			Ketamine and propofol	*Ketamine and dexmeditomidine*	*Total*
Houpt overall 3	5	Count	15	5	20
		% within group	100.0%	33.3%	66.7%
	6	Count	0	10	10
		% within group	0.0%	66.7%	33.3%
Total		Count	15	15	30
		% within group	100.0%	100.0%	100.0%

Chi-square tests

	Value	*df*	*Asymp. sig. (2-sided)*
Pearson Chi-square	15.000	1	0.000
N of valid cases	30		

Table 7: Modified Aldrete's recovery scale for consciousness—comparison between the two groups

Crosstab					
			Group		
			Ketamine and propofol	*Ketamine and dexmeditomidine*	*Total*
Consciousness	0	Count	3	6	9
		% within group	20.0%	40.0%	30.0%
	1	Count	12	9	21
		% within group	80.0%	60.0%	70.0%
Total		Count	15	15	30
		% within group	100.0%	100.0%	100.0%

Chi-square tests			
	Value	*df*	*Asymp. sig. (2-sided)*
Pearson Chi-square	1.429	1	0.232
N of valid cases	30		

The Modified Aldrete's recovery scale was measured at the end of the procedure to assess the recovery status of the patient. The scale measures activity, respiration, circulation, consciousness, and color. Student *t* test between the two groups showed insignificant difference in the recovery scale with *p* value of >0.05 for all the components of Modified Aldrete's recovery scale (Table 7).

Discussion

Some children are cooperative while some are not. Lack of cooperation from the child adversely affects the quality and duration of the treatment which can last a negative effect on the children as well as the parent. It is an arduous task to manage those uncooperative children in the dental setup.

Classical, nonpharmacological behavior management techniques do not always succeed. In such situations, pharmacological techniques would be the apt choice for pain-free dental care. Pharmacological behavior management techniques include different levels of sedation (including the commonly used misnomer "conscious sedation") and general anesthesia. The choice depends on multiple factors related to patient, dental set up, and the providers.[15]

The different levels of sedation, i.e., minimal, moderate, and deep sedation, have different potential for complications and hence results in need for different levels of monitoring.[16] Although a large number of drugs/groups of drugs produce sedation, each of them have different clinical effects and it is essential to understand safety level with individual drugs or combination of drugs. Drugs producing sedation have a potential to suppress the protective reflexes of the airway and can also alter the hemodynamic status. These effects can lead to serious complications, such as airway obstruction, hypoxia, aspiration, delayed recovery, etc.

Preliminary studies have suggested that midazolam is an effective premedication for children when administered intramuscularly, rectally, intranasally, or orally.[17–20] Intravenous sedation has a faster onset with excellent quality of sedation. Having a venous cannula is a prerequisite for IV sedation which also helps in management of complications.

In our study, we have used midazolam premedication as a common factor in all the two groups because it does not cause significant respiratory depression and has excellent safety profile. Midazolam has anxiolytic, amnesic (anterograde amnesia), sedative, and anticonvulsant properties. Ketamine was selected because of its excellent analgesic effects associated with sub-anesthetic doses (1 mg/kg). Propofol was used in this study at subanesthetic dose to produce sedation. In one of the group (KP group), combination of ketamine and propofol in a dose of 1 mg/kg each was used.[6,7] Dexmedetomidine is a newer centrally acting α2 agonist that provides sedation and analgesia without significant respiratory depression. Ketamine and dexmedetomidine act synergistically to provide excellent sedation with minimal side effects, and hence they are combined in a group called KD in a dose of 1 mg/kg and 1 µg/kg, respectively.[8,9]

In dental treatment, local anesthetic (LA) is administered first, which leads to pain and stress. The aim, therefore, is to provide optimal sedation and anxiolysis at time of injection of LA.

The heart rate in KP group was significantly higher and was similar to the study done by Kramer and Ganzberg.[21] The highest heart rate was seen in the KP group which can be explained by stimulatory effect of ketamine on cardiovascular system. Interestingly, this was seen despite combining it with propofol which is otherwise known to produce bradycardia. It appears to be because of the low dose of propofol used in this study.[9] In contrast, KD group had significantly lower heart rate compared to both the other groups. This is due to the cardiovascular effects of dexmedetomidine which also attenuates the cardio stimulatory effects and psychological effects of ketamine and is effective in attenuating the central nervous system effects of ketamine.[22] In our study, we did not see any cardio stimulatory effects of ketamine in children who were given the dexmedetomidine–ketamine combination, similar to the findings of Canpolat.[23]

The systolic blood pressure was significantly higher in the KP group compared to KD group. This was similar to the study done by Canpolat et al. and is due to cardio stimulatory effects of ketamine in KP group, whereas it was lower in KD group predominantly due to depressive effects of dexmedetomidine in KD group.[9]

There was statistically significant difference in the sedation levels after 5 minutes of administration of the drug measured by Modified Ramsay Sedation score. The sedation was of higher quality in KD group than KP group. But in both the groups, the recovery was delayed at the end of procedure. Similar findings were observed by Canpolat et al.[9]

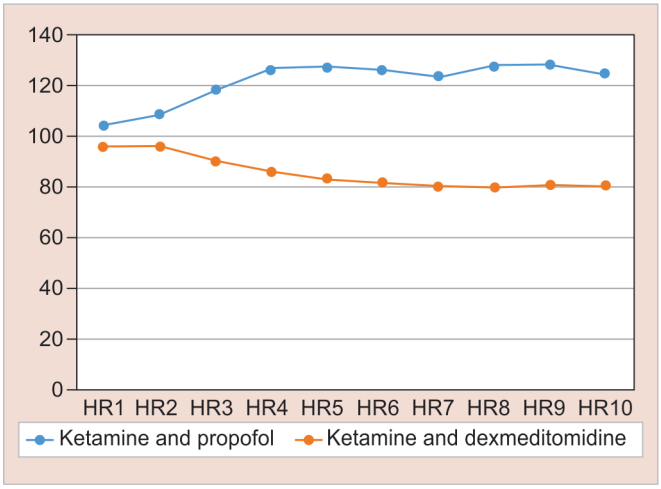

Fig. 1: Heart rate

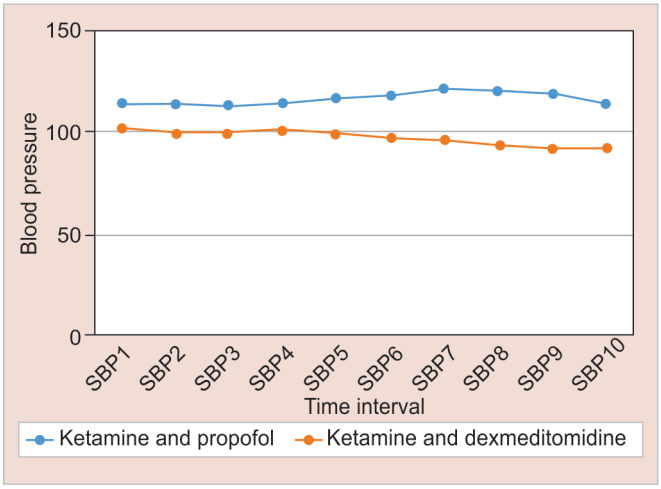

Fig. 2: Systolic blood pressure

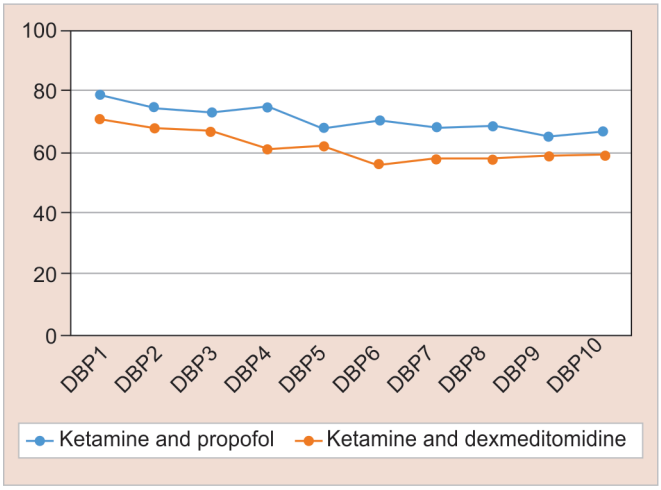

Fig. 3: Disatolic blood pressure

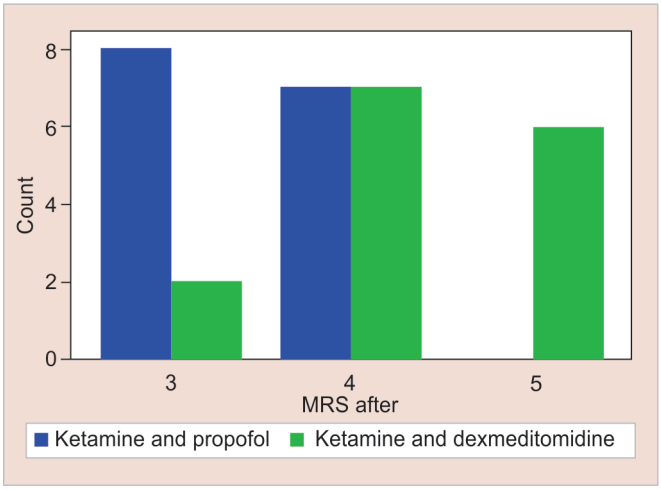

Fig. 4: Modified Ramsay sedation score after the treatment

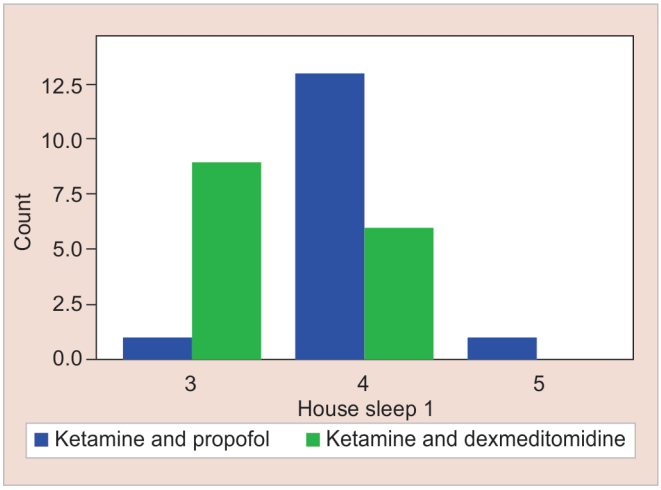

Fig. 5: Houpt score for sleep immediately after the delivery of drug

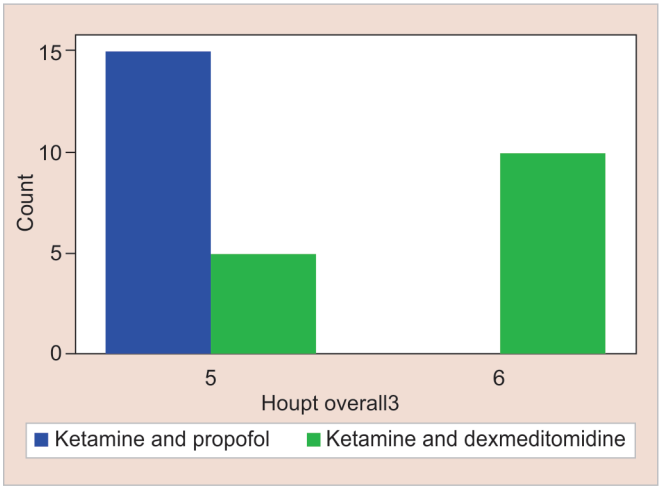

Fig. 6: Houpt overall sedation score after the treatment

Houpt sedation score for movement and crying shows similar scores between the groups, and it was insignificant. There was statistically significant difference in the Houpt sedation score for sleep, immediately after the delivery of drug (*p* value 0.007). The KD group had better sedation than the KP group (Score of 5). The Houpt score for overall behavior showed no statistical significance, but the behavior of child was calm and controlled in KD group than KP group. Two children in KP group cried and interrupted the treatment. As the sample size is small, generalized statement cannot be made.

Modified Aldrete's recovery scale was recorded at the end of the procedure. The scale measured activity, respiration, circulation, consciousness, and color. There was no significant difference between both the groups (Figs 1 to 6).

It was observed that KP and KD group had delayed recovery. In all, 80% of children from KP group showed the score of 1, i.e., arousal on calling. The remaining 20% showed a score of 0, i.e., no response.

In the KD group, 60% of children showed the score of 1, and the rest showed the score of 0. The KD group had longer recovery time of about 45 minutes to 1 hour compared to KP group, but this was not statistically significant. Also, in KP and KD groups, patients were administered additional doses of ketamine (5 mg) which could have resulted in marginally prolonged recovery. These findings again are in accordance with those of canpolat.[9]

Five patients in the group KP had postoperative nausea and vomiting which in all cases was self-limiting. It was surprising as propofol has proven antiemetic properties and the side effects could be related to the constitutional differences between patients in their susceptibility to development of postoperative nausea and vomiting. No complications were seen with the KD group. Similar results were found in the study done by Wilson et al.[17]

Lack of any abnormal altered psychological behavior who received ketamine (KP and KD group) could be due to attenuation of adverse psychological effects of propofol or dexmedetomidine. Previous studies by Badrinath et al. have reported similar findings.[23]

Conclusion

Both the combinations of ketamine with propofol and dexmedetomidine provide sedation with adequate analgesia. Considering the overall levels of sedation achieved, perioperative adverse effects, recovery patterns, and interruptions in the treatment during the course of sedation, it can be concluded that a combination of ketamine with dexmedetomidine provides satisfactory and better-quality sedation for pediatric dental procedures. The choice remains with the dentist and anesthesiologist to decide the combinations, amount of drug to be delivered, and the route of administration.

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