Original Article

Comparison of Three Different Ketofol Proportions in Children Undergoing Dental Treatment

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Abstract

Aim and Background: Sedation is gaining popularity among dental procedures in children. Ketamine and propofol mixture, known as ketofol, is one of the promising choices in sedation protocols; however, there is no consensus on the exact ratio of ketamine plus propofol especially in dental practice. The aim of present study was to compare perioperative side effect profiles, recovery profiles, and satisfaction rates of both parents' and dentists' following three different ratio of ketofol mixtures in children undergoing dental treatment. **Materials and Methods:** Three study groups each containing 30 children scheduled for dental treatment were created. Following anesthesia induction with 5% sevoflurane, 50% nitrous oxide mixture in 50% oxygen, 1 mg/kg bolus ketofol dose was administered. Patients in Group 1 received ketofol as a 1:1 mixture, patients in Group 2 received 1:2 ketofol while in Group 3; 1:4 ketofol was administered at a constant dose of 100 μg/kg/min. Additional doses of the ketofol solution at the same concentration with infused solutions in groups (0.5 mg/kg from either 1:1, 1:2, or 1:4 proportions) were administered if required. Perioperative vital signs, side effects, postoperative side effects, recovery durations, parents' and dentists' satisfaction levels were compared between groups. **Results:** There were no significant differences between groups in terms of perioperative vital signs and side effects. Depth of sedation, dentists' satisfaction levels and postoperative side effects –myoclonus, hypersalivation and tachycardia were significantly higher in Group 1. Parents' satisfaction was highest in Group 3, however, necessity of additional doses and dissatisfaction of dentists' were found highest in this group. Mean duration of recovery recorded in Group 3 was shortest compared with other groups. **Conclusion:** Decreased ketamine doses in ketofol mixture was related with decreased side effect profile, high parents' satisfaction with fast recovery, however, dentists' satisfaction was lower. In this context, results of present study indicated that ketofol mixture of 1:2 ratio was more reliable choice than others when all investigated parameters evaluated simultaneously.

Keywords: *Dentistry, dentists' satisfaction, ketamine, ketofol, parents' satisfaction, propofol, sedation*

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Introduction

The diagnosis and treatment of dental problems in childhood are essential for lifetime oral and dental health. However, dental fear, personal temperaments, and insufficient cooperation frequently necessitate sedation or general anesthesia in this group of patients.[1] Although dental procedures are usually not as invasive as procedures related to other organ systems, considerable levels of pain and distress levels need to be managed

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successfully. Local anesthesia usually provides sufficient pain control during dental procedures. In addition, various sedation protocols with either inhalation agents or intravenous drugs alone or combined are commonly used in children undergoing dental procedures.[2] Nitrous oxide or sevoflurane are commonly used inhalation agents, whereas midazolam, propofol, and ketamine alone or the combinations of midazolam-ketamine, ketamine-propofol, and midazolam-ketamine are frequently used intravenous agents.[2-4] Sedation with single agent(s) often provides sufficient levels of unconsciousness. However, the combination of more than one agent can lead to lower rates of complications related to each drug. A ketamine-plus-propofol (ketofol) regimen is an example of balanced anesthesia with minimal respiratory depression, the dissociative anesthesia-features of ketamine-plus short acting, minimal sympathomimetic effect, short recovery, and the anti-emetic features of propofol.[5,6] Several studies investigated one or two mixtures of ketamine and propofol in various clinical/surgical situations. However, no consensus has been reached on the most reliable proportion of these two drugs.[5-7]

In this study, we aimed to investigate and compare the anesthetic efficacy of three ketamine-propofol mixtures in various proportions on children undergoing dental treatment. We evaluated hemodynamic parameters; preoperative complications; sedation levels; recovery time; dentists', and parents' satisfaction rates; postoperative side effects; and the anxiety levels of children.

Materials and Methods

After obtaining local ethical committee approval at Gazi University, 90 ASA I pediatric patients with dental anxiety and uncooperative behavior (Frankl Behavior Rating Scale >3) undergoing dental treatment between the ages of 6 and 12 were enrolled in the study. The written informed consent of the parents was obtained. The exclusion criteria included having advanced respiratory and cardiac problems, mental motor retardation, a history of undergoing any invasive procedure under general anesthesia/sedation, epilepsy, seizures, allergic reactions, and taking medication for any reason 48 hours or less before the procedure. Preoperative premedication was not provided before anesthesia induction. Electrocardiograms (ECGs), peripheral oxygen saturation (SpO_2), and end-tidal CO_2 were monitored. Supplemental oxygen at a flow of 3-4 L/min was administered through a nasal cannula for all patients.

Three study groups were randomly created, sevoflurane (5%)[8] and nitrous oxide (50%) inhalation anesthesia used for induction and following anesthesia induction vascular accesses were established on one hand in all patients. After 1 mg/kg bolus ketofol dose, Group I received ketofol as a 1:1 mixture of ketamine and propofol at a constant dose of 100 μg/kg/min. Each syringe contained 4 mg ketamine and 4 mg propofol per milliliter. Group 2 received a 1:2 mixture of ketamine and propofol, with each syringe consisting of 2 mg ketamine and 4 mg propofol per milliliter. Group 3 received a 1:4 mixture of ketamine and propofol, with each syringe containing 1 mg ketamine and 4 mg propofol per milliliter. The following parameters were recorded: the basal findings at the third minute and then every 5 minutes during the operation, the heart rate (HR), the systolic blood pressure (SBP), the diastolic blood pressure (DBP), peripheral oxygen saturation, the Observers' Assessment of Alertness/Sedation Scale (OASS), and the duration of the anesthesia/operation. Additional doses of the ketofol solution at the same concentration with infused solutions in groups (0.5 mg/kg from either 1:1, 1:2, or 1:4 proportions) were administered when the HR or SBP was 20% higher than basal levels. Hypoxia, respiratory depression, bronchospasm, laryngospasm, myoclonus, hypersalivation, tachycardia, and allergic reactions were recorded as side effects. Postoperative nausea, vomiting, hallucinations, respiratory, and hemodynamical complications were also recorded. A respiratory rate lower than eight breaths/minute and/or an apnea period longer than 15 seconds were defined as respiratory depression. Meanwhile, having SpO_2 levels lower than 90% was defined as hypoxia. The Vancouver score was used for evaluating recovery levels. At the end of the dental treatment, the anesthesiologist assessed the satisfaction levels of the dentist and parents who were blinded to the anesthetic technique using a 3 point satisfaction scale (1 = dissatisfied, 2 = nearly satisfied, and 3 = completely satisfied). The study's primary end points were patients' sedation levels, the complication rates, the recovery times, and the dentists' and parents' satisfaction levels.

Statistical analysis

All statistical analyses were performed using SPSS 24.0 packet program. Normally distributed variables were compared using one-way analysis of variance (ANOVA). Significant results were compared using Post-hoc analysis of Tukey HSD test. Non-normally distributed data were compared using Kruskal-Wallis test. The Chi-square analysis was used to evaluate categorical variables. A *P* value of less than 0.05 was accepted as statistically significant.

Results

Demographical data of all patients, ASA status and Frankl Behavior Rating Scale results were shown in Table 1.

Table 1: Demographical data of patients in groups (mean±standard deviation, *n*)

	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
Age (year)	8.20±1.96	8.40±1.88	8.53±1.86	0.786
Gender (male/female)	14/16	16/14	16/14	0.837
Body weight (kg)	29.63±6.08	29.77±6.14	29.96±4.97	0.975
ASA (I/II)	24/6	24/6	23/7	0.935
Frankl Behavior Scale (3/4)	11/19	12/18	12/18	0.954

ASA=American Society of Anesthesiologists

Table 2: Mean operation time, administered additional doses in groups (mean±standard deviation, *n* [%])

	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
Operation time (min)	37.13±6.28	36.20±5.16	36.07±4.66	0.695
Additional doses used in patients (no/yes)	27/3 (10.0)	21/9 (30.0)	16/14 (46.7)*	χ^2=10.595 0.005

*P<0.05: Compared with Group 1

Table 3: Data regarding perioperative side effects in groups, *n* (%)

	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
None	22 (73.3)	25 (83.3)	26 (86.7)	χ^2=3.535
Respiratory depression	3 (10.0)	3 (10.0)	3 (10.0)	0.473
Desaturation	5 (16.7)	2 (6.7)	1 (3.3)	

Table 4: Data regarding postoperative side effects recorded in groups, *n* (%)

	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
No/yes	14 (46.7)/16 (53.3)	21 (70.0)/9 (30.0)	23 (76.7)/7 (23.3)*	χ^2=6.498 0.039
None	14 (46.7)	21 (70.0)	23 (76.7)	χ^2=6.748
Myoclonus	8 (26.7)	4 (13.3)	3 (10.0)	0.345
Hypersalivation	3 (10.0)	2 (6.7)	2 (6.7)	
Tachycardia	5 (16.7)	3 (10.0)	2 (6.7)	
Nausea/vomiting	3 (10.0)	2 (6.7)	2 (6.7)	0.345

*P<0.05: Compared with Group 1

There was no statistically significant difference between demographical data of patients (P > 0.05) [Table 1].

Mean operation time recorded in three study groups were found similar (P = 0.695) [Table 2]. Mean duration of operations were 37.13 ± 6.28 min, 36.20 ± 5.16 min, and 36.07 ± 4.66 min [respectively, Table 2]. Additional mean ketofol doses used in groups were significantly different from each other (P = 0.005). In Group 3, additional doses were used in 14 patients (46.7%), where additional doses were used in only 3 patients (10.0%) in Group 1 (X^2 = 10.569, P = 0.001) [Table 2].

There was no statistically significant difference in terms of perioperative side effects recorded in three study groups [Table 3].

Ratios of postoperative side effects recorded in groups were significantly different from each other [Table 4]. In Group 1, postoperative side effects were seen in 16 patients (53.3%), where in Group 3 number of side effects that recorded were 7 (23.3%) X2 = 6.498, P = 0.039). Ratio of side effects recorded in Group 1 was significantly higher than that recorded in Group 3 (X^2 = 6.099, P = 0.027), [Table 4].

Parents' satisfaction levels were found different from each other when compared between study groups. Satisfaction levels were higher in Group 3 compared with Group 1 and Group 2 [Table 5].

Also dentists' satisfaction levels noted in Group 1 were significantly higher than those noted in other study groups [Table 5].

There was no significant difference between groups regarding peripheral oxygen saturation levels (P > 0.05) [Table 6].

There was no significant difference between groups regarding systolic and diastolic arterial pressure values (P > 0.05) [Tables 7 and 8, respectively]. Mean HR values of patients in study groups were found similar (P > 0.05) [Table 9].

OAAS was the tool for assessing sedation levels during the present study. We found that mean OAAS scores at 5., 15., 25., 30., 35., and 40th minutes in Group 3 were significantly higher than those recorded in Group 1 [Table 10]. Additionally, OAAS score at

Table 5: Parents' and dentists' satisfaction levels related with different ketofol doses used in study groups, *n* (%)

	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
Parents' satisfaction levels (1/2/3)	0 (0.0)/8 (26.7)/22 (73.3)	0 (0.0)/14 (46.7)/16 (53.3)	9 (30.0)/17 (56.7)/4 (13.3)*,#	χ^2=37.341<0.0001
Dentsits' satisfaction levels (1/2/3)	12 (40.0)/18 (60.0)/0 (0.0)	0 (0.0)/10 (33.3)/20 (66.7)	0 (0.0)/6 (20.0)/24 (80.0)*,#	χ^2=68.931<0.0001

*P<0.05: Compared with Group 1, #P<0.05: Compared with Group 2

Table 6: Peripheral oxygen saturation levels of patients in study groups (mean±standard deviation)

Time (min)	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
0	96.63±1.47	96.67±1.35	96.67±1.35	0.994
3	97.33±0.66	97.23±0.73	97.23±0.63	0.802
5	97.40±0.93	97.33±0.84	97.37±0.76	0.955
10	97.20±0.76	97.10±0.71	97.10±0.66	0.822
15	97.03±1.10	97.30±0.75	97.30±0.70	0.393
20	97.27±0.91	97.27±0.83	97.27±0.78	0.999
25	96.93±1.14	97.00±1.08	96.97±1.06	0.973
30	96.93±1.64	96.87±1.63	96.87±1.63	0.984
35	97.13±0.82	97.07±0.83	97.07±0.83	0.937
40	97.17±0.95	97.13±0.94	97.13±0.94	0.988

Table 7: Systolic arterial pressure values (mmHg) of patients in study groups (mean±standard deviation)

Time (min)	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
0	106.27±9.14	106.30±9.15	105.00±8.17	0.810
3	107.50±7.76	108.47±6.90	107.97±6.67	0.871
5	113.57±15.13	114.63±14.21	114.20±13.97	0.960
10	108.37±5.67	109.20±4.83	108.50±6.45	0.768
15	108.37±8.02	109.17±7.53	109.43±7.17	0.851
20	109.80±8.07	111.17±6.03	110.23±7.10	0.667
25	112.80±6.96	113.37±6.24	112.45±5.64	0.927
30	107.23±10.54	107.97±10.35	107.63±9.86	0.962
35	111.43±8.72	110.70±8.51	110.60±8.38	0.918
40	110.53±8.80	110.00±8.88	108.20±9.28	0.864

Table 8: Diastolic arterial pressure values (mmHg) of patients in study groups (mean±standard deviation)

Time (min)	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
0	66.23±2.96	66.20±3.01	66.03±2.87	0.961
3	66.20±4.23	66.37±4.25	66.60±3.94	0.932
5	68.23±3.30	68.80±2.20	68.77±2.13	0.640
10	69.80±5.29	70.50±4.07	69.45±5.35	0.787
15	69.20±4.43	69.77±3.36	69.60±3.25	0.832
20	66.10±3.99	66.90±2.62	67.03±2.43	0.453
25	70.43±3.40	70.73±2.88	70.47±2.53	0.911
30	69.76±4.64	70.07±4.17	69.60±3.33	0.904
35	70.00±4.68	71.45±4.95	70.43±3.96	0.900
40	68.53±3.97	69.75±4.27	68.67±4.29	0.925

35th minutes recorded in Group 3 was significantly higher than that recorded in Group 2 ($P = 0.003$).

The Vancouver Sedative Recovery Scale (VSRS) was used to evaluate recovery profile of patients following ketofol sedation. Mean VSRS scores at 10. and 15th minutes in Group 3 were significantly lower than those recorded in Group 1 ($P = 0.016$ and $P < 0.0001$, respectively). VSRS score at 10th minutes in Group 2 was significantly lower than that recorded in Group 1 ($P = 0.003$) [Table 11].

Table 9: Heart rate values (rate/per minute) of patients in study groups (mean±standard deviation)

Time (min)	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
0	100.47±10.77	99.20±9.00	99.20±9.00	0.841
3	114.17±7.24	110.43±6.43	110.20±6.37	0.145
5	113.90±5.86	112.70±5.32	112.53±5.19	0.574
10	115.13±5.46	113.43±6.07	112.83±5.88	0.287
15	115.37±5.50	114.17±4.40	113.80±4.10	0.350
20	115.67±5.50	114.13±6.03	113.37±5.15	0.271
25	114.97±5.95	114.90±6.11	114.20±5.68	0.857
30	115.57±4.68	115.53±4.73	115.13±4.44	0.921
35	115.67±4.20	115.27±4.51	114.47±5.45	0.921
40	115.93±4.26	115.33±5.01	113.35±6.01	0.854

Table 10: Mean observers' assessment of alertness/sedation scores recorded in groups (mean±standard deviation)

Time (min)	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
0	5.00±0.00	5.00±0.00	5.00±0.00	-
3	1.07±0.25	1.10±0.30	1.23±0.43	0.136
5	1.07±0.25	1.20±0.41	1.40±0.50*	0.007
10	1.17±0.38	1.13±0.35	1.33±0.48	0.129
15	1.07±0.25	1.10±0.30	1.30±0.47*	0.026
20	1.10±0.30	1.23±0.43	1.20±0.41	0.381
25	1.07±0.25	1.17±0.38	1.37±0.49*	0.012
30	1.00±0.00	1.17±0.38	1.27±0.45*	0.011
35	1.00±0.00	1.03±0.18	1.23±0.43*,#	0.002
40	1.00±0.00	1.10±0.30	1.30±0.47*	0.002

*P<0.05: Compared with Group 1, #P<0.05: Compared with Group 2

Table 11: Mean Vancouver Sedative Recovery Scale scores and recovery times recorded in study groups (mean±standard deviation)

	Group 1 (*n*=30)	Group 2 (*n*=30)	Group 3 (*n*=30)	*P*
5 min	5.70±0.47	5.50±0.51	5.53±0.51	0.250
10 min	2.90±0.30	2.37±0.49*	1.97±0.49*,#	<0.001
15 min	1.80±0.66	1.50±0.51	1.30±0.47*	0.003
30 min	1.23±0.43	1.07±0.25	1.07±0.25	0.076
45 min	1.00±0.00	1.00±0.00	1.00±0.00	-
60 min	1.00±0.00	1.00±0.00	1.00±0.00	-
Mean recovery time (min)	22.7±4.5	17.5±2.8*	15.8±2.3*	<0.05

*P<0.05: Compared with Group 1, #P<0.05: Compared with Group 2

Discussion

In this study, we compared the complication rates, recovery durations, and parents' and dentists' satisfaction levels related to conscious sedation with different mixtures of ketofol administration. The main finding of the study was that a ketofol mixture at a 1:2 ratio resulted in an acceptable recovery profile after adequate

intraoperative sedation levels, high dentists' satisfaction levels, and sufficient parents' satisfaction levels. In the 1:4 group (Group 3), the highest parents' satisfaction levels were noted because of early recovery. However, the dentists were not satisfied due to the uncontrolled movements of the patients during the treatment process. In the 1:1 group (Group 1), the dentists were fully satisfied due to the lack of uncontrolled movements and signs of awakening. However, in this group, the recovery time was significantly prolonged, and the parents were displeased and worried during the recovery phase. However, beyond the dentists' and parents' satisfaction levels, we did not record any respiratory, cardiac, or other systematic complication necessitating additional emergent medication or intervention. Perioperative side effect –respiratory depression and desaturation only-ratios were similar between groups. This final finding of the study is important because the safety of patients is mandatory and of the highest priority in all medical situations.

Respiratory depression secondary to anesthetic agents is especially important in dental procedures under sedation because the oral cavity is the working area of dentists, so respiratory depression is more likely to occur because of the aspiration of saliva, blood, or dental equipment. In addition, manipulations of the gums and of the hypopharynx, for example, may lead to laryngospasm or bronchospasm. In such a situation, the minimal respiratory depressor effect of ketamine becomes prominent. However, the amelioration of the swallowing function and other protective reflexes after sedation are important because of the risk of continuing minimal bleeding. At this point, a fast recovery achieved through propofol becomes important in dental treatment.[9] Propofol is a commonly used sedative-hypnotic agent with a rapid onset, a short duration of action, an anti-emetic quality, and amnestic properties without an analgesic effect. Propofol exerts dose-related respiratory depression, bradycardia, and hypotension. Although dose titration is possible, these side effects can lead to significant adverse events.[10,11] However, ketamine has rapid-onset dissociative anesthesia with a strong analgesic effect and minimal respiratory or cardiovascular depressor effects. This demonstrates that ketamine is a preferred agent for procedural sedation and analgesia in many clinical situations, including in dental procedures in children.[12] The commonly encountered side effects of ketamine are tachycardia with or without hypertension, hallucinations, nausea, vomiting, and a delayed recovery following sedation.[9] In the present study, there was no significant difference between groups in terms of tachycardia and hypertension which were known side effects of ketamine administration. Ketamine dose was highest in Group 1 and lowest in Group 3. Different doses of ketamine may lead tachycardia and/or hypertension. However, mean HRs at all time points were found similar between groups. We suggest that lower doses of ketofol used in Group 3 may lead mild sedation-which proven by increased number of additional doses used in this group-and awareness with tachycardia. Increased HRs related with mild sedation may result in indifferences between mean HRs.

When an early recovery and the anti-emetic properties of propofol are combined with the minimal cardio-respiratory depressor effects and strong analgesic effect of ketamine, ketofol administration seems to be a reliable alternative sedation technique. Several studies revealed that the combination of these two drugs leads to significant dose decrements for both agents.[11] Several studies investigated various ketofol mixtures with various proportions of ketamine and propofol. However, no consensus has been reached on an optimal ketamine/propofol ratio. In these studies, a wide range of mixtures include an equal ratio of ketamine and propofol (1:1) to one part of ketamine and 10 parts of propofol (1:10) were assessed. Rapeport *et al*.[6] reported that a 1:1 ketamine/propofol combination resulted in safe and reliable sedation in high-risk patients. However, in this study, only four patients were each administered a ketofol infusion, and this number of patients is too small for making a clear decision. Erden *et al*.[13] compared one part of ketamine plus one part of propofol, and one part of ketamine and two parts of propofol in children undergoing interventional radiological procedures. They concluded that a 1:1 mixture of ketamine and propofol is safer and more comfortable than 1:2 mixtures without any adverse respiratory events. However, in this study, the authors administered ketofol combinations as bolus doses, not as continuous infusions, so the findings of this study can be questionable when compared with our findings. A constant and continuous dose may lead to a more steady-state sedation level with fewer additional bolus doses as indicated in our study. Daabis *et al*.[14] reported safe and effective sedation using 0.6 mg/kg bolus ketofol followed by 100 micg/kg/min continuous ketofol infusion (either 1:1 or 1:4 [ketamine: propofol]) in 100 children undergoing various interventional procedures, such as oesophagoscopy, endoscopy, bone marrow aspiration, rectoscopy, and liver biopsy. The authors concluded that higher doses of ketamine resulted in a delayed recovery with postoperative nausea and hallucination.

In terms of dental procedures under sedation, several studies reached different conclusions regarding ketofol sedation. In a study conducted by Kramer

et al.,[15] propofol remifentanil and propofol ketamine combinations were compared in patients aged 18-40 undergoing third molar tooth extraction. The authors concluded that although similar levels of hemodynamical and respiratory stabilization were achieved with both combinations, a prolonged recovery time and dentists' dissatisfaction were reported in the group of patients receiving propofol plus ketamine. Canpolat *et al*.[4] investigated various sedation regimens for children undergoing dental treatment procedures with ketamine alone at a dose of 1 mg/kg, propofol alone at a dose of 1 mg/kg, and ketamine plus propofol at doses of 0.5 mg/kg. Patients were randomly divided into three groups, and all patients received the single induction doses described above. Additional doses of 1/2 of the induction doses were administered if an RSS below 4 was noted. The authors revealed similar hemodynamical and respiratory satisfaction levels. However, they also found that propofol alone was superior compared with the others in terms of the short recovery time, preserving postoperative nausea and vomiting, and the surgical satisfaction level. In the present study, overall ratio of postoperative side effects recorded in Group 1 was significantly higher than that recorded in Group 3. Myoclonus, tachycardia, hypersalivation, and nausea/vomiting were four side effects recorded at postoperative period. However, there was no significant difference between groups in terms of these side effects when statistical analysis done individually for each side effect. We suggest that postoperative side effect profiles of three different mixtures of ketofol in the present study indicate safe, comparable, and sufficient sedation levels with ketofol.

To the best of our knowledge, no study compares single induction doses versus the continuous infusion of ketofol in the literature. However, in a review that Jouguelet-Lacoste *et al*.[16] compared the effects of repeated doses of ketamine versus a low-dose continuous ketamine infusion on postoperative pain and concluded that a continuous infusion regimen is superior in terms of pain control. In our study, we used the continuous infusion of three ketofol doses. In this way, we avoided the dose-related sympathomimetic effects of ketamine and the cardio-respiratory depressor effects of propofol.

Previous studies investigating the effects of ketofol on children reported a mean recovery time ranging from 6.5-–23 minutes. However, studies investigating the mean recovery time following the administration of ketamine alone reported an interval of 25–103 minutes,[17-19] whereas others investigating the mean recovery time after sedation with propofol alone reported an interval of 8–93 minutes.[20-22] In our study, we found longest recovery period following 1:1 ketofol administration. In contrast, recovery periods in Group 2 and Group 3 were shorter than recorded in Group 1. Shah *et al*.[23] compared ketamine alone versus ketofol sedation in children undergoing orthopaedic reductions. In the ketofol group, patients received induction doses of ketamine 0.5 mg/kg and 0.5 mg/kg propofol followed by 0.5 mg/kg propofol alone every 2 minutes during the procedure. In the ketamine-alone group, patients received induction doses of 1.0 mg/kg ketamine followed by 0.25 mg/kg ketamine alone at every minutes when required. They found that the recovery period following the ketamine-alone group was 12 minutes, whereas it was 10 minutes in the ketofol group. In addition, the postoperative nausea and vomiting rate was significantly lower in the ketofol group (2% versus 12%). In a review, Slavik and Zed[24] evaluated a large database related with the effects of ketofol sedation (ketamine: propofol proportions ranged from 1:2 to 1:10). The authors concluded that the optimal dose was not clear and that propofol alone was not superior to ketofol in terms of hemodynamic and respiratory outcomes. Furthermore, higher doses of ketamine in a mixture were related to more adverse events, including a prolonged recovery, postoperative nausea, and vomiting with hallucinations as indicated in the present study. Our findings support the previous findings of Slavik and Zed and others in terms of the close relationship among higher ketamine doses, increased overall postoperative side effects. However, myoclonus, tachycardia, hypersalivation, and nausea/vomiting ratios in groups found similar when analysis was done individually for each parameter. In addition, the mean recovery time recorded in 1:1 ketofol group (Group 1) was significantly longer than those recorded in other groups (22.7 min versus 17.5 min and 15.8 min, respectively ($P < 0.05$) [Table 11]. Also in Group 1 mean VSRS points at 10th and 15th minutes were significantly higher than those recorded in Group 3. Additionally in Group 3, VSRS points at 10th minutes were significantly lower than those recorded in Group 2, however, at 15th minutes mean VSRS points were similar between Group 2 and Group 3. These results indicated slow recovery time with high dose ketamine (in Group 1 and Group 2 compared with Group 3) in ketofol mixture. Andolfatto and Willman[25] evaluated data regarding effectiveness, side effects, and the recovery time following ketofol in a 1:1 mixture (10 mg/ml ketamine and propofol in the same syringe) in 219 patients aged from 8–16 admitted to the emergency department. In this large-scale study, respiratory support was needed in only three cases without additional adverse events, and the mean recovery period was 14 minutes. Physicians and parents were highly satisfied following ketofol sedation.

Injection pain is a well-known side effect of propofol, and several local anesthetics, such as prilocaine and lidocaine, can be administered previously. da Silva *et al*.[10] reported only two of 20 cases with injection pain during ketofol sedation in children undergoing bone marrow aspiration and lumbar punction. In addition, Shah *et al*.[23] reported injection pain in none of the 136 patients undergoing ketofol sedation for orthopaedical reductions. Similarly, in our study, no injection pain was noted in all 90 patients.

Conclusion

Three mixtures of ketofol used in dental practice provided sedation procedures with acceptable respiratory and hemodynamic adverse event profiles. However, increased doses of ketamine (noted in the 1:1 mixture group) are closely related to increased overall (total) postoperative side effects (myoclonus, tachycardia, and hypersalivation) and prolonged recovery time. However, lower doses of ketamine in ketofol administration (noted in the 1:4 mixture group) led to lower RSS levels with lower dentists' satisfaction and increased additional bolus doses. We recommend the continious infusion of a 1:2 ratio of ketamine: propofol mixture sedation for dental procedures in children because of the associated safe, stable intraoperative sedation levels, reliable lower postoperative side effect profile, short recovery time, and adequately high dentists', parents', and anesthetists' satisfaction levels.

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Conflicts of interest

There are no conflicts of interest.

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