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Original Article

A comparison of the effects of ketamine-midazolam and ketamine-propofol combinations on vital signs of non-cooperative children with dental diseases in a crossover study with repeated measurements: The Bayesian approach

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Abstract

Background: Vital parameters must be monitored during sedation. This study aimed to evaluate the effects of ketamine-midazolam (KM) and ketamine-propofol (KP) combinations on the heart rate (HR) and oxygen saturation (SPO_2) of non-cooperative children. The model parameters were estimated using the Bayesian approach.

Methods: The data were collected in a double-masked crossover study with repeated measurements (CSWRM). Twenty-two non-cooperative children 3–6 years old were included, and the linear mixed model was adopted for data analysis. The Bayesian estimation of the parameters and their 95% credible interval were calculated in SAS 9.4.

Results: The mean HR of KM recipients compared to KP recipients was significantly different by 4.47 beats per minute (bpm). The mean HR in KP was lower than KM's, but SPO_2 was not significantly different.

Conclusion: Although the two drug combinations did not differ in SPO_2, they differed in HR. As such, the KP combination is recommended.

Keywords: Ketamine, Midazolam, Propofol, Non-cooperative children, Crossover trial, Bayesian approach

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Introduction

Reports from 195 countries and territories from 1990 to 2017 show that oral disorders are the most common cause of disease, and tooth decay contributes more than other problems to oral disorders.[1] According to the World Health Organization's (WHO's) report, the prevalence of tooth decay in children is 60–90%.[2] The overall prevalence of caries in permanent and deciduous teeth in Iranian children is 78.6% and 62.8%, respectively.[3]

During the treatment of dental problems, some children do not cooperate with their dentists for different reasons, and therefore, special arrangements must be made. One such arrangement is treatment under sedation. In general, sedation is a method of controlling stress and unwanted reactions using drugs, which differs from general anesthesia.[4] Unlike anesthesia, a lower dose of drugs is used, and the person can breathe spontaneously without assistance.[5] However, the choice between anesthesia and sedation depends on factors such as the anatomy of the respiratory tract,[6] the child's age, the number of teeth that need treatment, the child's general health status,[7] and the time required for the treatment,[8] the determination of which is the anesthesiologist's responsibility.

So far, different drugs have been used alone or in combination, and different doses have been recommended for sedation. The most effective way to use sedatives is

intravenous injection because the absorption of drugs in the child's body is faster.[5] The comparison and review of sedatives with different combinations and doses is still a major research goal. The sedative should ideally maintain the stability of vital signs.

Ketamine is used in lower doses as a sedative with sleep-inducing and analgesic properties. Using it alone can cause side effects such as vomiting, nausea, anxiety, and hallucinations. A reduction in the dose of ketamine and using it in combination with other sedatives can reduce the side effects.[9] Propofol and midazolam are two other commonly used sedatives that do not have analgesic properties. Propofol has hypnotic properties, and its short half-life is a major advantage because it reduces recovery time. The primary objective of the use of midazolam is to reduce anxiety, and it has benefits such as a quick onset of effect and a low probability of loss of consciousness. Midazolam's disadvantages are memory disorder and the possibility of side effects (increased irritability and restlessness) in the patient.[5] Different medications are combined to reduce the dosage of the drugs and benefit from their respective advantages.[4, 9-12] The combination of ketamine with midazolam (KM) and propofol (KP) for sedation has been investigated in some studies, but no crossover study with repeated measurements (CSWRM) was found. In Dal's study, the aim was to compare the effectiveness and safety of KM and KP combinations on adults in transbronchial needle aspiration guided by intrabronchial ultrasound (EBUS-TBNA), blood pressure, heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SPO_2), Ramsay sedation score (RSS), and cough severity were evaluated.[9] Bayraktaroglu and colleagues' study was designed for healthy adults undergoing colonoscopy to compare the effects of KM and KP on hemodynamic parameters, intraocular pressure, and endoscopic and patient satisfaction.[10] Adiban and colleagues' study was conducted on children aged 1 to 14 years undergoing upper endoscopy to investigate the sedation effects of KM and KP. In their study, blood pressure, HR, and RSS were recorded and analyzed.[11] To compare the sedation effects of ketamine, KM, and KP on children undergoing adenotonsillectomy surgery, Fattahi-Saravi et al conducted a study. In this study, objective pain score, modified Aldert improvement score, and Richmond restlessness-sedation scale (RASS) were checked.[12]

CSWRM analysis using a mixed linear model provides useful interpretations for variables on a continuous scale. The Bayesian approach outperforms the classical approach in estimating parameters in a mixed linear model when the sample size is small.[13] The current study aimed to compare the effect of two drug combinations, KM and KP, on the HR and SPO_2 of non-cooperative children with dental diseases using the Bayesian approach in a linear mixed model.

Methods and Materials

This was a double-masked, crossover clinical trial with repeated measurements in each period. First, the study was registered in the Iranian Registry of Clinical Trials (identifier: IRCT20090506001882N10), and permission was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1400.1176). The children's parents provided written informed consent for participation.

The sample size was calculated for 22 children based on a type-one error of 0.05, a type-II error of 0.2 (80% statistical power), and Cohen's effect size of $d=0.6$ (an effect size between moderate and large). Twenty-two healthy children (ASA 1) aged 2 to 6 years who were non-cooperative (completely negative on the Frankel scale according to two dentists), visited the Fellowship Department of Shahid Beheshti Dental School, and required two similar dental treatment sessions were non-randomly (conveniently) selected. Two treatment sessions were planned to be similar in terms of treatment time, the type of anesthesia, and the type of treatment. The exclusion criteria were systemic diseases, a history of allergy to drugs, colds, and blocked nasal passages during the treatment session, and failure to complete two treatment sessions. The second treatment session was scheduled 2 to 3 weeks after the first.

Midazolam 0.3 mg/kg was given to the children orally as premedication 30 minutes before the intravenous injection of the drugs. The aim was to compare two treatment regimens of intravenous KP (2–2 mg/kg, respectively) and intravenous KM (2–0.2 mg/kg, respectively). In both groups, atropine 0.02 mg/kg was used to reduce secretions. Oxygen was administered through a nasal cannula at a rate of 5 liters/min. During the treatment, if needed, a maintenance dose of propofol at a dose of 150 µg/kg/min and ketamine at a dose of 10–15 µg/kg/min was given to the KP and KM treatment groups, respectively.

Before the premedication injection, the patient's HR and SPO_2 were recorded in each session. In both sessions, SPO_2 and HR were recorded by the hospital's multi-purpose monitoring device during venipuncture, after local anesthetic injection, every 15 minutes during treatment (15 minutes and 30), and post-treatment.

The linear mixed model was adopted to compare the two drug combinations. Baseline measurements were also made in each period and entered as covariates into the model for handling. Due to the lack of exact times for measuring the response during anesthesia injection and discharge, the time was considered categorically and entered as a dummy variable into the model. Assume that the continuous response of the i-th participant in sequence j, whose t-th measurement is in period p, is represented by y_{et} ($i=1, ..., NJ, j=1,2, p=1,2, t=1,...,k$) and $X_{treatment}$, X_{period} and $X_{sequance}$ and $X_{baseline}$ indicate the treatment, period, sequence, and baseline variables, respectively. X_{time}

is a time dummy variable vector. Therefore, the model included the fixed effects of treatment (β_1), period (β_2), sequence (β_3), and baseline (β_6). The two-parameter vectors $\beta_5^{'}$ and $\beta_5^{'}$ correspond to the vector of dummy variables time and time x treatment interaction. The random effects in the model include the effect of the i -th participant in sequence j (s_{ij}), the effect of the i-th participant in sequence j in the p-th period (w_{ijp}), and the effect time for the i-th participant (b_{ij}). The measurement error is indicated by ε_{ijpt}. The linear mixed model for the CSWRM is as follows:

$$y_{ijpt} = \beta_0 + \beta_1 X_{treatment} + \beta_2 X_{period} + \beta_3 X_{sequance} + \beta_4{}' X_{time} + \beta_5{}' X_{time} X_{treatment} + \beta_6 X_{baseline} + s_{ij} + w_{ijp} + b_{ij}{}' X_{time} + \varepsilon_{ijpt}$$

The Bayesian estimation of the parameters and their Bayesian 95% confidence interval were calculated in SAS 9.4.

Results

Nine girls and 13 boys with an average age of 3.6 and a standard deviation (SD) of 0.97 years were recruited. Twelve randomly received the KP combination, and 10 participants received the KM combination in the first period. The treatments were changed in the second period. The mean and SD by sequence, treatment, and time are presented for HR in Table 1. Table 2 provides the same information for SPO_2. Of the five times that the HR was measured after administering the drug combination in the first sequence (KP in the first period and KM in the second period), the mean HR of KM was higher than that of KP in three points in time. The KM combination consistently led to a higher mean HR than the KP combination in the second sequence (KM in the first period and KP in the second period), except at the time of venipuncture. Figure 1 shows that in both treatments and periods, the mean HR at the baseline is lower than at

Table 1. Mean (SD) of HR by sequence, drug combination, and time

Sequence	Treatment	Time					
		Baseline	Venipuncture	Injection	15 min	30 min	Discharge
KP-KM[a]	KM	107.00 (10.72)	126.42 (8.46)	129.42 (13.79)	130.58 (14.96)	128.42 (12.41)	121.08 (11.42)
	KP	111.67 (11.57)	121.08 (9.07)	130.00 (13.40)	127.58 (8.74)	120.83 (9.72)	122.08 (8.05)
KM-KP[b]	KM	113.11 (8.79)	126.60 (8.38)	141.00 (12.81)	141.80 (11.31)	136.00 (11.71)	126.56 (8.69)
	KP	111.89 (8.37)	128.11 (10.71)	136.20 (14.85)	131.10 (12.21)	128.10 (11.93)	121.89 (7.34)

[a] Sequence where participants received KP in the first period and KM in the second period.
[b] Sequence where participants received KM in the first period and KP in the second period.

Table 2. Mean (SD) of SPO_2 by sequence, drug combination, and time

Sequence	Treatment	Time					
		Baseline	Venipuncture	Injection	15 min	30 min	Discharge
KP-KM[a]	KM	97.33 (1.50)	97.75 (1.29)	99.42 (0.79)	99.17 (1.34)	99.75 (0.62)	96.75 (0.75)
	KP	97.33 (1.07)	97.75 (1.06)	98.92 (1.44)	98.83 (1.59)	99.17 (1.11)	96.75 (1.54)
KM-KP[b]	KM	97.78 (1.20)	97.60 (0.84)	99.40 (1.26)	99.60 (1.26)	99.80 (0.63)	97.11 (1.05)
	KP	97.67 (0.87)	98.00 (1.25)	99.50 (0.85)	99.20 (1.23)	99.50 (0.97)	96.22 (0.97)

[a] Sequence where participants received KP in the first period and KM in the second period.
[b] Sequence where participants received KM in the first period and KP in the second period.

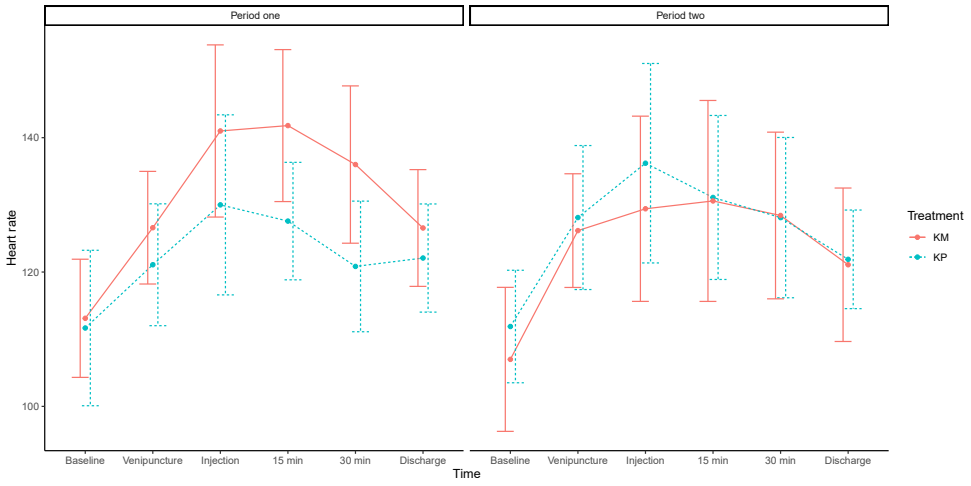

Figure 1. The mean trend and SD for HR in two periods. The blue line corresponds to the KP, and the red line corresponds to the KM combination

all times, and the changes have similar patterns. Based on Figure 2, the trends of variations in mean SPO_2 for both treatment groups in each period are almost the same.

The time x treatment interaction effect was not significant ($P>0.05$) for HR or SPO_2; as a result, the effect of the two treatments on both variables over time was not opposite (output not presented). This confirms the visual information in Figures 1 and 2. Due to the non-significance of interaction effects, they were removed from the model, and a model without interaction effects was fitted. The results of the model for HR are given in Table 3. The carry-over effect and period were not significant, according to Table 3. Therefore, the non-significance of the carry-over effect enables us to check the treatment effect. Adjusting for the effect of the baseline measurement, in a KM recipient, HR was, on average, 4.47 beats per minute (bpm) lower than a KP recipient. This difference was statistically significant ($P<0.05$).

It can also be concluded that, by adjusting for the effect of the baseline measurement, KM recipients had a mean HR 4.47 bpm lower than KP recipients. With 95% confidence, the mean HR of KP recipients was at least 1.41 bpm and at most 7.71 bpm lower than KM recipients. The mean HR of participants at the time of local anesthesia injection and 15 minutes after was, respectively, 8.55 bpm and 7.70 bpm higher (significantly) than the venipuncture

Table 3. Bayesian estimation of parameters from the linear mixed model with HR and SPO2 response variables; the estimates related to the HR response variable and the estimates related to the SPO2 response variable

Parameter	HR				SPO2			
	Est.	SD	BayCI		Est.	SD.	BayCI	
Intercept	62.51	18.22	25.95	96.94	81.87	8.56	64.70	98.01
Sequence								
AB[a]	-2.96	4.17	-11.31	5.05	-0.09	0.24	-0.59	0.39
BA	Reference							
Period								
Two	0.36	1.63	-3.00	3.40	0.04	0.19	-0.33	0.40
One	Reference							
Treatment								
A[b]	-4.47*	1.60	-7.71	-1.41	-0.23	0.18	-0.59	0.14
B	Reference							
Time								
Injection	8.55*	2.26	4.25	12.88	1.46*	0.24	0.99	1.92
15 min	7.70*	1.90	3.90	11.29	1.34*	0.23	0.89	1.78
30 min	3.42	2.26	-1.15	7.73	1.71*	0.24	1.25	2.18
Discharge	-1.66	2.30	-6.05	2.86	-1.09*	0.24	-1.53	-0.62
Venipuncture	Reference							

* Significant at the 5% level .
[a] AB sequence received KP in the first period and KM in the second period, and the BA sequence was vice versa.
[b] A is the KP combination, and B is the KM combination.
Estimate (Est.), standard deviation (SD), with Bayesian 95% confidence interval (BayCI).

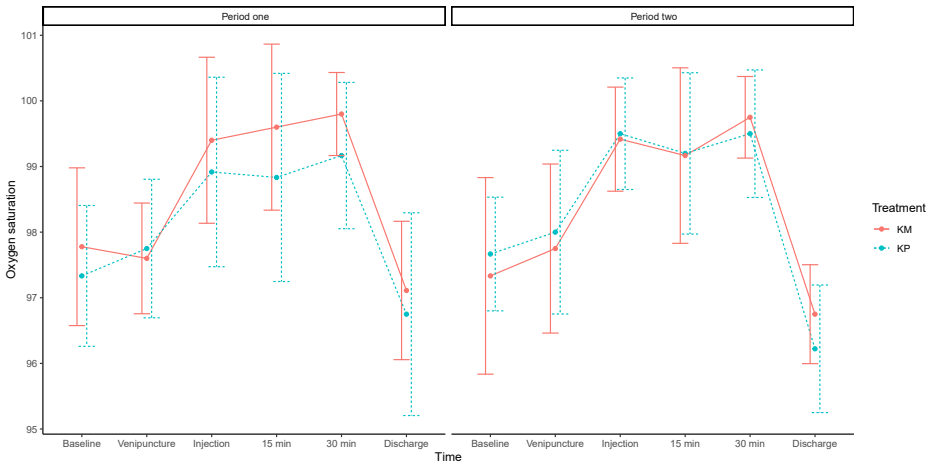

Figure 2. The mean trend and SD for SPO_2 in two periods. The blue line corresponds to KP, and the red line corresponds to the KM combination

time for both treatments. The mean HR 30 minutes after administration and post-treatment was not significantly different compared to the venipuncture time for both treatments.

The results of fitting the model for the SPO_2 are listed in Table 3. After adjustment for the effect of the baseline measurement, there was no significant difference between the effects of the two treatments on the SPO_2 of the participants who experienced both treatments. In other words, there was no significant difference between KP and KM combinations regarding the mean SPO_2. The mean SPO_2 for a participant at the time of anesthesia injection and 15 minutes and 30 minutes after the start of the treatment was respectively 1.46%, 1.34%, and 1.71% higher (significantly) than it was at the venipuncture time in both treatments. The mean SPO_2 for a participant at the time of injection was 1.09% lower (significantly) than it was at discharge time for both treatments.

Discussion

Using an efficient sedative can create good memories for children, relieve their fear and anxiety, and make it easier for them to visit the dentist in the future. A key research goal is to compare sedatives in terms of their effect on vital signs and hemodynamic variables. This paper investigated the effects of KM and KP on HR and SPO_2 with a CSWRM. Due to the small sample size, the Bayesian approach was adopted in the linear mixed model to estimate the effects better. Our findings showed no significant interaction effect between time and treatment for either of the dependent variables. That is, the profile of changes in HR and SPO_2 during the time is the same for both combinations of KM and KP. Also, no significant carry-over and period (sequence) effects were observed. The main effect of time was significant for both the dependent variables, while the main effect of treatment was significant for HR and nonsignificant for SPO_2. Modeling the data showed that the trend of SPO_2 was the same for both combinations; SPO_2 did not change significantly with the change in medication and remained somewhat stable during the treatment after venipuncture. The effect of KM on the respiratory system is small, but propofol may harm the respiratory system.[5] However, this finding can be due to using a nasal cannula during treatment for all patients. If the nasal cannula had been used only when needed, the study's results might have been different. Similar findings were observed by Dal and Canpolat, who used nasal cannulas. Dal investigated sedation with midazolam followed by ketamine versus KP.[9] Canpolat recruited children 3–9 years old to compare propofol, ketamine, and propofol-ketamine combination.[14] In both studies, there was no significant difference between the groups in terms of SPO_2 at any measurement time,[9, 14] while in a study that did not use a cannula, the reduction in SPO_2 was greater in KP than KM.[15]

We found that the HR trend was the same for both combinations, and the mean HR for KP was significantly lower than it was for KM. The predominant effect of sympathetic and non-sympathetic properties in midazolam and propofol increase the HR and does not change it during sedation compared to the baseline; however, HR during sedation with propofol was significantly lower than with midazolam.[16] On the other hand, ketamine can increase HR due to its sympathomimetic property,[14] and when combined with other sedatives, it can reduce the effects of this property.[5] These effects of drugs and their compounds on HR may be the main reason for our findings. In Dal's study, the HR in the KM group was significantly higher than in the KP group, only 10 minutes after the intervention.[9] In the comparison of KM and PM, HR was higher in the KM combination;[17] nevertheless, no significant difference was observed in comparing the mean HR with propofol, KP, and PM.[18] These results are consistent with our findings.

Previous studies have compared KP and KM at different doses. It has been shown that both KM and KP combinations reduce salivary flow compared to pre-sedation, but there was no difference between these two compounds during treatment.[19] Using KM and KP for sedation during colonoscopy of adults (18 to 60 years old), no significant difference in intraocular pressure was reported during the treatment. Still, in both groups, there was a significant difference in the first minute of sedation compared to pre-treatment. In the first minute of sedation, the mean blood pressure (MBP) of KP recipients was lower than that of KM recipients, and it was significantly reduced compared to pre-treatment. At other times (3, 6, and 9 minutes after sedation and post-treatment), there was no difference compared to each other and compared to pre-treatment.[10] In a study that used these two compounds for sedation in endobronchial ultrasound-guided transbronchial needle aspiration, there was no significant difference between the MBP of the two groups.[9] In children (under 12 years old), the number of times the MBP decreased or increased by more than 20% compared to the baseline at 5, 10, 15, 20, and 25 minutes post-administration for both drug combinations did not markedly differ.[15]

There was a difference in the mean diastolic and systolic pressure in children (1 to 14 years old). Regarding diastolic pressure, there was a significant difference between the two treatment groups, while there was no difference in systolic pressure.[11] Despite the use of different doses in the two combinations in the literature, the recovery time was shorter for KP recipients.[9,15,20,21]A study by Adiban et al revealed that KM resulted in better sedation at all times (5, 10, 30, and 60 minutes post-administration) based on RSS,[11] but in another study, KM was better than KP only at the 35th minute.[9] Fattahi-Saravi et al showed that KP recipients had lower scores on the RASS.[12] In

another study, where the level of sedation was based on the Observer Assessment of Alertness and Sedation Scale, there was no difference between the two compounds.[10] This difference in the results may be due to the difference in the scales. As a result, both combinations were found to be effective in different studies.

For data analysis in a CSWRM, a linear mixed model makes it possible to determine the rate of variations in the response variable by changing the treatment type and adjusting the effect of covariates. In a linear mixed model, the correlation structure of the data can be characterized by random effects.[22] By adopting the appropriate random effects of a CSWRM, the correlation structure between the responses can be considered. Unfortunately, after preparing the CSWRM data, parameter estimation with the Bayesian approach in the linear mixed model was more time-consuming than the classical approach. It was necessary to change the number of iterations and the number of burnings several times to model the data in this study in order to achieve convergence. In future studies, the analysis of responses with a non-continuous scale or the simultaneous analysis of a combination of responses will be conducted to compare sedatives.

Using a statistical model, which can assess many hypotheses simultaneously instead of statistical tests, is one of our strengths. Using the Bayesian approach, which is more appropriate for a small sample size instead of the frequency (classic) approach, is another strength of this research. Our participants were from only one governmental center, so we recommend conducting this investigation with patients from various clinics and centers. We used the noninformative prior normal distribution (0, 1000) for the model's parameters and the noninformative inverse gamma distribution (0.01, 0.01) for the variance's parameters. Our suggestion is to use other noninformative distributions. Also, we modeled two dependent variables separately, known as the univariate approach. A good idea can be fitting the model using multivariate or join methods.

Conclusion

Our findings generally showed that the mean HR is significantly higher when using KM for sedation of non-cooperative children needing dental treatment than with KP. However, mean SPO_2 does not significantly differ between the two drug combinations. As a result, the KP combination is preferable in terms of HR.

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Competing Interests

None.

Data Availability Statement

The data of this study are available from the corresponding author upon request.

Ethical Approval

the study was registered in the Iranian Registry of Clinical Trials (IRCT20090506001882N10), and permission was obtained from the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1400.1176).

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