Dental Research Journal

Original Article

Comparative evaluation of bispectral index system after sedation with midazolam and propofol combined with remifentanil versus ketamine in uncooperative during dental procedures

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ABSTRACT

Background: Proper analgesic agents should be used in combination with sedative agents. Remifentanil is a synthetic narcotic/analgesic agent with a short duration effect and decreases the risk of apnea during recovery. Bispectral index system (BIS) is a new noninvasive technique for the evaluation of the depth of sedation. The aim of present clinical trial was to evaluate and compare the efficacy of intravenous sedation with propofol/midazolam/remifentanil (PMR) in comparison to propofol/midazolam/ketamine (PMK) for dental procedures in children 3-7 years of age.

Materials and Methods: In this clinical trial, 32 healthy uncooperative children who were candidates for dental treatments under sedation were randomly divided into two groups. Intravenous sedation was induced with PMR in one group and with PMK in the other group. After injection and during procedure BIS index, heart rate and respiratory rate, blood pressure, and oxygen saturation was evaluated every 5 min. After the procedure, recovery time was measured. Data were analyzed with ANOVA, Friedman, Wilcoxon, and *t*-test.

Results: The BIS value was significantly low in ketamin group ($P = 0.003$) but respiratory rates and heart rates were same in both groups with no statistical difference ($P = 0.884$, $P = 0.775$). The recovery time was significantly shorter in remifentanil group ($P = 0.008$ and $P = 0.003$).

Conclusion: It can be concluded that intravenous sedation technique with PMR combination induces effective and safe sedation, with less pain and more forgetfulness and a shorter recovery time for children 3-7 years of age during dental procedures.

Key Words: Bispectral index, ketamine, midazolam, propofol, remifentanil

Received: April 2015
Accepted: September 2015

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INTRODUCTION

Intravenous sedation is the second most comfortable, effective, and the safest technique after inhalation sedation; however, the technique should be used only by trained personnel.[1] Sedative techniques do not involve intubation, contrasting general anesthesia and the recovery period is short.[2] There are basically two techniques available for intravenous sedation: Use of

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www.ncbi.nlm.nih.gov/pmc/journals/1480

How to cite this article: Eshghi A, Mohammadpour M, Kaviani N, Tahririan D, Akhlaghi N. Comparative evaluation of bispectral index system after sedation with midazolam and propofol combined with remifentanil versus ketamine in uncooperative during dental procedures. Dent Res J 2016;13:1-6.

only one medication, which is usually benzodiazepine and a combination of several medicines.[1] In sedation, it is of the utmost importance to achieve analgesia. Due to the limitations of the use of local anesthetic agents such as overdose and reaching the toxic levels of medications, proper analgesic agents should be used in combination with sedative agents.[3]

The most commonly medications used in sedation are ketamine, midazolam, and propofol.[4-6] Ketamine has an analgesic effect but may cause complications during recovery, including severe listlessness, nausea, delirium, nystagmus, and severe muscle spasms. It is contraindicated in patients with a history of convulsions.[5,6] In contrast, propofol does not have an analgesic effect but may increase the risk of respiratory depression, body irritation, crying, and coughing during the procedure and anxiety during recovery, with no nausea.[6,7] Midazolam has no analgesic effect but may induce forgetfulness after the procedure.[7] Remifentanil is a synthetic narcotic/analgesic agent with a strong analgesic effect which decreases the risk of apnea during recovery; however, it has a short duration of effect.[8] Since it results in minor changes in cardiac waves and leads to rapid recovery, remifentanil is a good choice for cardiac and debilitated patients.[9,10]

Bispectral index system (BIS) is a new noninvasive technique for the evaluation of the depth of sedation and may be a proper technique for evaluation of children undergoing a sedative technique.[11,12] The electroencephalography (EEG) device reports the waves numerically in a range of 0-100, in which 100 indicates full consciousness and a value between 60 and 90 indicates adequate sedation.[13,14] These values should be in the range of 40-60 in general anesthesia, 60-70 in profound sedation, and 70-90 in moderate sedation.[14] There are only a few studies available on intravenous sedation of children for dental procedures. Combining medications results in the use of lower doses and the risks associated with medications decrease.[5-8,15] A combination of propofol, fentanyl and midazolam resulted in more effective sedation, with shorter recovery, compared to the use of propofol alone[15] and the use of a combination of propofol and remifentanil was safe, effective, and acceptable.[8] Regardingthe , inconsistent results of propofol[5-[8,12]. Remifentanil is a new medication and its combination with midazolam increases forgetfulness after the procedure compared to midazolam alone.[16] Further studies are needed to determine the best combination of drugs for sedation in children.[5-8,15,16] The present study was undertaken to evaluate and compare the efficacy of a combination of propofol/midazolam/ketamine (PMK) with that of a combination of propofol/midazolam/remifentanil (PMR) in sedating children during dental procedures by means of BIS technique.

MATERIALS AND METHODS

Participants

In the present prospective, double-blind clinical trial a total of 32 uncooperative children (one or two negatives based on Frankel behavioral rating scale[1]), aged 3-7, who referred to Department of Hospital Dentistry in Isfahan Dental School selected randomly. The inclusion criteria were healthy children who had no specific systemic disease and were in the category I of the American Society of Anesthesiology. At the time of sedation, children did not have a common cold or any airway problems. Patients with extraction or who needed dental work time more than 45 min were excluded. The sample size in each group was 16 subjects at a significance level of 0.05 and a power of 80% ($\alpha = 0.05$, $\beta = 0.20$), using the below formula. This was estimated to show a six difference in the mean of BIS index between the two groups.[10]

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})(\delta_1^2 + \delta_2^2)}{d^2} \quad \delta_1 = \delta_2 = \frac{0}{5} \quad d = 6$$

Sedation protocols and patient monitoring

After obtaining informed consent from the parents, they received the necessary instructions for the sedative procedures. All the patients were asked to refer in the morning, in a fasting state (at least 5 h not to eat by mouth or non per os), for the dental procedures which performed at Department of Hospital Dentistry, Isfahan University of Medical Sciences, Isfahan, Iran.

Randomization was carried out as follows: On the day of the procedure each subject was given a code of which only the anesthesiologist was aware. Neither subjects and nor other researchers were aware of codes. Patients were randomly divided into two groups based on the odd or even codes. In the group with even codes, propofol/midazolam/ketamine was administered intravenously in the following doses: Ketamine (0.5 mg/kg); propofol (0.5 mg/kg); and midazolam (0.01 mg/kg).

In the group with odd codes, midazolam/propofol/remifentanil was administered intravenously in

the following doses: Midazolam (0.01 mg/kg); propofol (0.5 mg/kg); and remifentanil were pumped intravenously at (0.1 μg/kg/min).

The depth of sedation, BIS, heart rate, the number of respirations, blood pressure, and oxygen saturation percentages were recorded every 5 min by the anesthesiologist. Therefore, a complete monitoring which is essential for general anesthesia or deep sedation was performed for both groups. The conditions for carrying out the procedure were evaluated by another researcher based on the Dental Sedation Teachers Group (DSTG)[17,18] scale and recorded in special data sheets. At the end of the procedure, each patient was monitored in the recovery room and the time needed for recovery was recorded. After achieving the necessary conditions for being discharged based on the postanesthetic discharge scoring system,[1] each patient was discharged based on thorough counseling and provision of a phone number for emergency calls.

Statistical methods

After collection of data the codes were deciphered and data were analyzed with SPSS (version 20 ,Chicago, IL, USA), using Friedman's and Wilcoxon's tests, ANOVA, *t*-test and Pearson's correlation coefficient. The level of the confidence interval was considered at 95%.

Ethical aspect

The protocol and consent form were approved by Research Committee of Isfahan University of Medical Science (code number 393398) and Registered in Iranian Registry of Clinical Trials (registration code #IRCT2015042512848N2). It should be noted that drug doses were completely based on medical literature, and careful patient care was provided during the work. Moreover, attempts to treat a child in ordinary dental appointment were not successful due to lack of cooperation, parents informed of the treatment under sedation, and written consent was obtained. Patients pay only the cost of dental treatments, and no additional charges would be incurred for this study.

Table 1: Demographics and the mean working time

Group	Mean age	Male	Female	Mean working time (min)
Remifentanil	1/20±3/72	7	9	8/53±39/62
Ketamin	1/75±5/50	8	8	9/73±40/83
P_v	0/037		0/9	0/742

RESULTS

Study population and mean total dose of drugs

A total of 32 children aged 3-7 years, consisting of 17 girls (52%) and 15 boys (48%), were included in the present study. The mean age of the subjects was 4.36 ± 1.6 years. *t*-test showed no significant differences in gender, duration of the procedures and body weights between the two groups [Table 1].

The bispectral index system values between groups

The mean BIS index in the remifentanil group 5 min after the initiation of sedation was 68.62 ± 10.24, which first decreased during the sedation time but began to increase approximately 20 min after the initiation of sedation, finally reaching 69.71 ± 4.57. In the ketamine group, the mean BIS index 5 min after initiation of sedation was 50.08 ± 8.39, which first decreased in a manner similar to that in the remifentanil group but increased with time and finally reached a value close to that at the initiation time. Analyses of covariance for the repeated data showed significant differences in BIS between the two groups ($P = 0.003$), with significantly higher BIS index values in the remifentanil group compared to the ketamine group during the whole procedures [Table 2].

The bispectral index system values intra-groups in different time of procedure

The BIS index values were compared at nine different time intervals separately in each group, demonstrating no significant differences between the remifentanil and ketamine groups (intra-group) in different time intervals ($P = 0.505$ and $P = 0.577$, respectively). In all the subjects in both groups the DSTG sedation score[18] at all the nine different time intervals was 5 (eyes closed, no response to mild physical stimuli) and therefore, the conditions for carrying out the

Table 2: The BIS index values at different time intervals of the study (in min) in the two groups

Group	Interval									*P*
	5	10	15	20	25	30	35	40	45	
Remifentanil	68.62±10.24	67.62±9.21	56.54±8.48	65.15±6.37	65.31±6.72	65.75±4.28	68±5.17	67.13±5.30	69.71±4.57	0.505
Ketamine	50.08±8.39	53.58±8.45	51.58±11.09	49.25±9.27	49.82±10.71	49.09±8.74	48.33±6.36	50.33±9.23	50±11.95	0.577

BIS: Bispectral index system.

procedures were deemed "good" in all the subjects (the patient fully cooperative and proper sedation).

Safety profile

The heart rates in the two groups were evaluated and compared with repeated-measures ANOVA, revealing no significant differences between the two groups ($P = 0.884$).

The respiratory rates were evaluated at nine different time intervals using repeated-measures ANOVA, and no significant differences were found between the two groups ($P = 0.775$).

In all the subjects in both groups, the oxygen saturation percentage (PO_2 saturation) at different time intervals was 97-100%, and in none of the subjects it decreased to levels below 97%.

Procedure-related times

The mean recovery times from the time of medication administration in the remifentanil and ketamine groups were 9.23 ± 2.77 and 30.83 ± 5.96 min, respectively. *t*-test revealed a significant difference between the two groups ($P < 0.001$). Pearson's correlation coefficient did not reveal any significant correlation between the duration of the procedure and the recovery time ($r = 0.255$, $P = 0.218$).

Satisfaction survey

No psychomimetic and other complications, including severe sleepiness, negative reactions, and respiratory depression, were observed while the child was in the dental operatory or in the recovery room. Only a few cases of severe nausea and vomiting were reported in a few subjects in the remifentanil group, which were resolved by prescribing plasil (metoclopramide).

DISCUSSION

In the present blind clinical trial, the PMR combination was significantly more effective ($P = 0.003$) and was associated with less recovery time than PMK ($P < 0.001$). To our knowledge, there are a limited number of studies have compared the two drugs, remifentanil and ketamine (alone or in combination with other drugs). Several studies have shown that incorporation of remifentanil shortens the recovery time, consistent with the results of the present study.[15,19-22]

However, Moerman concluded that the addition of remifentanil to propofol during spontaneous ventilation had no benefits compared with the use of propofol alone. Although the addition of remifentanil resulted in a dose reduction of propofol, using propofol alone accompany with less recovery time and better patient satisfaction.[9]

In the present study, there were no significant differences in heart rates and respiratory rates between the two groups. Several studies have been conducted about side effects of remifentanil or other opioids. However, there are many discrepancies in results. For example, one study reported that the side effects of remifentanil were not more than nonopioid drugs.[23] While others demonstrated that complications such as breathing and conscious reduction were observed in the use of remifentanil.[8,9] The combination of remifentanil with midazolam increases forgetfulness after the procedure compared to midazolam alone.[16] It seems that PMR combination had more satisfactory results than propofol/remifentanil.

BIS scores in the PMK group were lower at all the time intervals than those in the PMR group, and more profound sedation had been achieved in the PMK group. The results of the present study were somewhat close to other studies such as Kramer *et al*. who compared the sedative effect of the combinations of remifentanil/propofol and ketamine/propofol. They found that both groups had the same respiratory and cardiac complications; however, the duration of sedative effect and the time of recovery for the ketamine group were significantly higher than remifentanil.[24] Moreover, Berkenbosch *et al*. reported that the combination of remifentanil and propofol had a well sedative effect and fast recovery with no serious side effects.[25] The most commonly technique to evaluate the depth of sedation is to assess clinical signs such as patient movement and response to verbal and physical stimuli which principally depend on the patient's personal reports and are considered an indirect indicator of the effect of medications on the brain.[1] Although EEG is one of the most straightforward techniques to evaluate brain activity during sedation, this technique is difficult and costly. BIS is a new noninvasive technique for the evaluation of the depth of sedation and might be a proper technique for evaluation of children undergoing a sedative technique.[11,12] Studies have shown that a BIS score ≥60 indicates an appropriate depth of sedation, with no possibility of accidental awakening during the procedure,[26] which was also shown in the present study. In the remifentanil group, the subjects were in

a profound sedation state at different time intervals; however, in the ketamine groups, the subjects were in general anesthesia state at all the intervals. Such a situation might be explained by the fact that the individual physiologic responses of children to a fixed dose are different. In other words, despite the use of a fixed dose for sedation, some children go into general anesthesia and the results of the present study showed that such a possibility is definitely higher with ketamine compared to remifentanil. Therefore, ketamine and remifentanil should be used for general anesthesia and deep sedation in the presence of proper tools under monitoring. Since there were no side effects, such as respiratory muscles spasms, apnea during recovery and laryngeal ulcers due to the absence of intubation, in the sedation technique compared to general anesthesia technique, more extensive a comprehensive studies are suggested to evaluate intravenous sedation techniques for dental procedures. The administration of PMK for general anesthesia and PMR for sedation purposes could be suggested.

CONCLUSION

It can be concluded that intravenous sedation technique with a combination of midazolam, propofol, and remifentanil induces effective and safe sedation, with less pain and more forgetfulness and a less recovery time for children 3-7 years of age during dental procedures.

ACKNOWLEDGMENTS

The authors would like acknowledge to the staff at the Department of Hospital Dentistry in School of Dentistry, Isfahan University of Medical Sciences. This study was based on a thesis to be submitted to Dental School, in partial fulfillment of the requirements of Specialist in Pediatric Dentistry. This study was funded by Vise Chancellery for Research, (Grant number 393398, IUMS).

Financial support and sponsorship

Torabinejad Dental Research Center, Isfahan University of Medical Sciences.

Conflicts of interest

No one of those who were involved in conception, designing, planning, running trial, interpretation, drafting manuscript and submission are funded or supported by any manufacturer or any other related affairs organization.

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