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Comparison of the Effects of Midazolam-Ketamine or Midazolam-Propofol Combinations on Hemodynamic Stability, Patient Comfort, and Post-anesthesia Recovery in Children Undergoing Sedation for Magnetic Resonance Imaging Procedures

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Abstract

Background: Magnetic resonance imaging (MRI) requires complete immobility of the subject during the acquisition of each sequence, which is highly important for image quality. MRI may necessitate sedation, particularly in young children and in some adolescent and adult patients, although the ideal sedation procedure leading to minimal side effects with the highest patient comfort in children undergoing MRI procedures remains controversial. The aim of this study was to compare the effects of midazolam-ketamine and midazolam-propofol combinations on hemodynamic stability, patient comfort, and post-anesthesia recovery in pediatric patients undergoing sedation for MRI and also to determine the ideal sedation procedure with minimal side effects.

Materials and Methods: The retrospective study included 40 pediatric patients aged between 2 and 12 years with normal growth and an American Society of Anesthesiology physical status (ASA-PS) 1-2 who were sedated with a combination of midazolam-ketamine or midazolam-propofol for the MRI procedure. The 40 patients were divided into two groups based on the drug combination used for sedation: (I) midazolam-ketamine (M-K) ($n = 20$) and (II) midazolam-propofol (M-P) ($n = 20$). Demographic characteristics, duration of MRI procedure, total duration of procedure, MRI image quality, family satisfaction, peripheral capillary oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and Ramsay Sedation Score (RSS) scores were compared between the two groups.

Results: No significant difference was detected between the groups with regard to gender, duration of MRI procedure, and total duration of procedure. The MRI scanning quality was very good in 14 (70%) and moderately good in 6 (30%) subjects in the M-K group, whereas the scanning quality was very good in 9 (45%) and moderately good in 11 (55%) subjects in the M-P group. There were significant differences between the two groups at different times in terms of SBP, DBP, and HR

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values. No complication was observed in any patient and no patient required additional sedation throughout the procedure.

Conclusion: The midazolam-ketamine combination provided better hemodynamic stability than the midazolam-propofol combination, although the two combinations were similar with regard to patient comfort and post-anesthesia recovery.

Keywords: Midazolam, Ketamine, Propofol, Magnetic resonance imaging, Pediatric patient, Daily anesthesia

Background

Magnetic resonance imaging (MRI) is a non-invasive procedure commonly used for diagnostic purposes. MRI provides a significant advantage over other imaging techniques as it does not involve exposure to ionizing radiation. Moreover, MRI provides extensive information about anatomic structures and has an important place in the diagnosis of numerous diseases. MRI requires complete immobility of the subject during the acquisition of each sequence. Moreover, it may necessitate sedation, particularly in young children and in some adolescent and adult patients, as it is a semi-enclosed environment and has a long duration of operation and a high ambient noise level of up to 95 decibels (Kang et al. 2017). MRI scans usually take about 30-60 min depending on the part of the body being imaged (Schulte-Uentrop and Matthias 2010). Most of the children requiring an MRI scan have neurological symptoms such as epilepsy and mental retardation. On the other hand, although disabled children do not require higher doses of sedation compared to non-disabled children, they have a three-time higher risk of hypoxia under sedation (Schulte-Uentrop and Matthias 2010). These notions are of paramount importance for the patients undergoing sedation for MRI. In addition, the ultimate objective in the sedation undertaken in patients undergoing MRI procedures should be to ensure maximum patient safety, successful screening, and excellent image quality throughout the procedure.

The type of anesthesia administered in patients undergoing MRI is called daily anesthesia. Thanks to daily anesthesia, the patient can be sent home without requiring overnight hospitalization (Selçuk et al. 2013). The agents used for the induction of daily anesthesia are aimed to provide rapid sleep onset, maintenance of vital functions, and quick recovery from anesthesia. These agents do not cause any side effects such as nausea, vomiting, and dizziness and also require no premedication. Accordingly, daily anesthesia aims to maintain hemodynamic stability without harming the physiology and metabolism of the subject and also provides a safe and quick recovery from anesthesia, thus promoting patient comfort.

Ketamine causes dissociative anesthesia characterized by amnesia and analgesia. However, despite its wide confidence intervals, ketamine has several side effects such as hallucinogenic effects, stridor, and laryngospasm. To reduce these side effects, ketamine is often used in combination with benzodiazepines (McCarty et al. 2000;

Howes 2004). Propofol is a short-acting hypnotic agent with no analgesic properties. Propofol can be administered at a bolus dose of 1-3 mg/kg and is often preferred for painless interventions due to its short recovery time. However, it may lead to hemodynamic and respiratory side effects such as apnea, myoclonus, decreased blood pressure, and thrombophlebitis depending on the dosage (Smith et al. 1994; Kessler et al. 1996). At high doses, it may also lead to hypotension and respiratory depression. The use of propofol in combination with other sedatives provides a synergistic effect and allows the use of lower doses. Midazolam is a short-acting hypnotic-sedative benzodiazepine with anxiolytic, anticonvulsant, hypnotic, and amnesic properties. Midazolam is highly advantageous due to its fast onset of action (1-2 min when administered intravenously) and its short recovery period (30-60 min). Midazolam is also administered to prevent the side effects of ketamine and to provide a synergistic effect by allowing the effective use of propofol at low doses (Kang et al. 2017).

In this study, we compared the effects of midazolam-ketamine and midazolam-propofol combinations on hemodynamic stability, patient comfort, and post-anesthesia recovery in pediatric patients undergoing sedation for MRI. The second aim was to determine the ideal sedation procedure with minimal side effects.

Materials and Methods

Patient Population

The retrospective study included 40 pediatric patients aged between 2 and 12 years with normal growth and an American Society of Anesthesiology physical status (ASA-PS) 1-2 who were sedated with a combination of midazolam-ketamine or midazolam-propofol for the MRI procedure. Patients that received sedatives other than midazolam-ketamine and midazolam-propofol combinations and patients detected with significant abnormalities based on clinical examination, electrocardiogram (ECG), or laboratory parameters were excluded from the study. The sample size of the patient group was determined based on the sample sizes used in similar studies (Selçuk et al. 2013). To attain a 95% confidence interval, a minimum sample size of 20 subjects was required for each group. Accordingly, a total of 40 consecutive patients who met the inclusion criteria were included in the study. The 40 patients were divided into two groups

based on the drug combination used for sedation: (I) midazolam-ketamine (M-K) ($n = 20$) and (II) midazolam-propofol (M-P) ($n = 20$).

Diagnostic Imaging

Magnetic resonance imaging (MRI) was performed using a 1.5T MRI scanner (Philips Achieva, Netherlands) according to standard protocols. All the images were evaluated by a single radiologist. Subjective quality of the scans was evaluated using a three-grade scale: 1 = very good (perfect scanning), 2 = moderate (scan completed), 3 = poor (scan uncompleted).

Drug Administration

Sedation was performed by the same anesthesia team in each patient. Before transferring to the MRI room, a venous cannula (B. Braun, Melsungen, Germany) was inserted in a suitable forearm vein. The M-K group received 1.5 mg/kg ketamine (Ketalar, 50 mg/ml, 10 ml; Pfizer, Sandwich, UK) and 0.1 mg/kg midazolam (Dormicum, 1 mg/ml, 5 ml; Deva Holding, Istanbul, Turkey) and the M-P group received 1 mg/kg propofol (Propofol-Lipuro, 10 mg/ml, 20 ml; B. Braun, Melsungen, Germany) and 0.1 mg/kg midazolam (Dormicum, 1 mg/ml, 5 ml; Deva Holding, Istanbul, Turkey) intravenously. Patients were placed in supine position with a roller under their shoulders. Continuous monitoring of vital signs including peripheral capillary oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) was performed with an MRI-compatible anesthesia monitor. Throughout sedation, oxygen was delivered at 2 L/min with a face mask and continuous end-tidal carbon dioxide monitoring was performed. As the sedation protocols involve risks of respiratory complications when performed with spontaneous breathing, the equipment necessary for emergency resuscitation such as laryngeal mask, endotracheal tubes, masks, airway, pediatric laryngoscope set, sedatives and general anesthesia drugs, and aspirator devices were made available in the MRI room.

Procedures

Demographical findings, total duration of procedure (including anesthesia and imaging), duration of MRI procedure, MRI scanning quality, family satisfaction (Table 1), and Ramsay Sedation Score (RSS) (Table 2) were recorded for each patient. SpO_2 , SBP, DBP, and HR were recorded every 5 min. The beginning and end of each procedure were recorded after providing appropriate sedation. After the procedure, the patients were transferred to the post-anesthesia care unit (PACU) and were continuously monitored for nausea and vomiting, agitation, pulse rate, and respiratory status until discharge to the ward. Post-anesthesia recovery was measured using the Aldrete Scoring System which rates

Table 1 Family satisfaction (3-point rating)

1: Very satisfied
2: Moderately satisfied
3: Not satisfied

sedation on a 0-10 scale according to the patient's activity, oxygen saturation, consciousness, respiration, and circulation.

Patient Data

Patient data were retrieved from the hospital database and the anesthesia reports of the patients.

Statistical Analysis

All data were analyzed using SPSS 17.0 for Windows (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, United States). Continuous data were expressed as mean \pm standard deviation (SD) and categorical data were expressed as percentages. Continuous variables were compared using Mann-Whitney U test and categorical variables were compared using chi-square test. A p value of <0.05 was considered significant.

Results

The M-K group included 10 (50%) men and 10 (50%) women and the M-P group included 13 (65%) men and 7 (35%) women. The two groups were similar in terms of age, body weight, height, duration of MRI procedure, total duration of procedure, ASA status, MRI scanning quality, family satisfaction, and RSS scores ($p > 0.05$). In terms of family satisfaction, 14 (70%) patients in the M-K group and 9 (45%) patients in the M-P group were revealed to be very satisfied. Moreover, the patients in the M-K group were clinically more comfortable compared to the patients in the M-P group, although no significant difference was established. RSS scores were used to determine the sedation levels of the patients. Accordingly, the RSS scores measured during MRI ranged between 1 and 5 in the M-K Group and between 2 and 4 in the M-P group (Table 3). Mean Aldrete score was 9.59 ± 0.68 (range, 7-10) in the M-K group and 9.63 ± 0.60 (range,

Table 2 Ramsay Sedation Scale (RSS)

The Ramsay Sedation Scale	
Point	Clinic
1	Awake, not comfortable and/or crying
2	Awake, calm, watching the surroundings
3	Sleepy but responds to verbal stimuli
4	Sleepy but responds immediately to glabellar tactile stimuli
5	Sleepy but responds slowly to glabellar tactile stimuli
6	Not responding to stimuli

Table 3 Demographic and clinical characteristics

		Midazolam-Ketamine	Midazolam-Propofol	<i>p</i>
Sex	Male (<i>n</i>)	10 (50%)	13 (65%)	0.337
	Female (<i>n</i>)	10 (50%)	7 (35%)	
Age (mean ± SD) (years)		3.1 ± 1.68	4.75 ± 3.55	0.068
MR procedure time (mean ± SD) (min)		17.5 ± 11.41	13.75 ± 2.75	0.161
Total procedure time (mean ± SD) (min)		22.15 ± 11.66	19.5 ± 3.59	0.338
Weight (mean ± SD) (kg)		13.8 ± 4.13	17.9 ± 8.38	0.057
ASA (<i>n</i>)	I:13		I:14	0.25
	II:7		II:6	
MRI scanning quality (<i>n</i>)	1:14 (70%)		1:9 (45%)	0.114
	2:6 (30%)		2:11 (55%)	
	3:0		3:0	
Family Satisfaction (<i>n</i>)	1:14 (70%)		1:9 (45%)	0.114
	2:6 (30%)		2:11 (55%)	
	3:0		3:0	
RSS (min-max)		1-5	2-4	0.826

ASA American Society of Anesthesiologists physical status classification, RSS Ramsay Sedation Score, MRI magnetic resonance imaging, *n* Number of patients

7-10) in the M-P group. Mean duration of PACU stay was 18.12 min in the M-K group and 18.86 min in the M-P group. No significant difference were observed between the two groups with regard to consciousness ($p > 0.05$). Patients with an Aldrete score of 9 and over were transferred to the ward. No complication was observed in any patient throughout the procedure.

The SBP values recorded at min 1, 5, and 10 after sedation were similar in both groups ($p > 0.05$). However, the SBP values recorded at min 15, 20, 25, and 30 were significantly lower in the M-P group compared to the M-K group ($p < 0.05$) (Table 4). Similarly, the DBP values recorded at min 1, 5, 10, 15, 20, and 25 after sedation were similar in both groups ($p > 0.05$). Nevertheless, the DBP value recorded at min 30 was significantly lower in the M-P group compared to the M-K group ($p < 0.05$) (Table 5). On the other hand, no significant difference was found between the groups in terms of oxygen saturation after sedation ($p > 0.05$) (Table 6). Similarly, no significant

difference was found between the two groups with regard to HR values after sedation ($p > 0.05$) (Table 7). No complication was observed in any patient after sedation. With the dose scheme we used, the drugs produced adequate sedation throughout the MRI procedure and no patient needed additional sedation throughout the procedure. Moreover, no antidote was administered in any patient during the recovery period and no complications such as cardiac arrest, apnea, laryngospasm, vomiting, cough, tachycardia, and increased oral secretions were observed in any patient throughout the procedure. As the procedure was completed with no complications, the procedure was considered successful.

Discussion

Sedation is frequently required in outside the operating room interventions. The MRI procedure is one of the most difficult procedures in anesthetic practice, mainly because the procedure requires the use of MRI-compatible equipment such as peripheral pulse oximetry, ECG device, non-invasive blood pressure monitoring device, end-tidal CO₂ monitor, aspirator, defibrillator, and anesthesia machine. Throughout the imaging process, the subject is required to remain immobile to ensure good image quality (Özdamar et al. 2010). To achieve this, some subjects require an adequate level sedation, particularly children. The primary characteristics of an effective sedative drug include an adequate sedation depth and minimal side effects (Frankville et al. 1993). Common sedative agents used for the MRI procedure include thiopental, propofol, ketamine, midazolam, etomidate, and fentanyl (Starkey and Sammons 2011). Of these, midazolam is the

Table 4 Systolic blood pressure values

	Midazolam-Ketamine	Midazolam-Propofol	<i>p</i>
Min 1	113.95 ± 6.7	114.15 ± 7.82	0.931
Min 5	114.05 ± 5.7	111.15 ± 7.63	0.213
Min 10	113 ± 5.43	109.45 ± 9.8	0.165
Min 15	115.6 ± 11.14	106.95 ± 8.98	0.01
Min 20	113.65 ± 4.61	105.35 ± 8.64	0.001
Min 25	114.4 ± 4.79	105.35 ± 9.03	0.000
Min 30	114.6 ± 5.08	104.75 ± 9.64	0.000

SBP systolic arterial pressure, SD standard deviation
Values are given as mean ± standart deviation (SD)

Table 5 Diastolic blood pressure values

	Midazolam-Ketamine	Midazolam-Propofol	<i>p</i>
Min 1	72.45 ± 7.05	72.15 ± 7.09	0.894
Min 5	70.85 ± 8.02	66.5 ± 7.7	0.089
Min 10	69.55 ± 6.99	64.75 ± 8.5	0.059
Min 15	68.9 ± 8.05	63.55 ± 7.5	0.036
Min 20	69.1 ± 8.18	62.4 ± 7.61	0.011
Min 25	68.85 ± 8.27	62.85 ± 7.83	0.024
Min 30	70.25 ± 7.18	62.3 ± 7.09	0.001

DBP diastolic blood pressure, SD standard deviation
Values are expressed as mean ± SD

most commonly used agent in preschool children and has been shown to have hypnotic, sedative, amnesic, anticonvulsant, anxiolytic, and respiratory depression effects (Akçay et al. 2018). Accordingly, the present study aimed to compare the effects of midazolam-ketamine and midazolam-propofol combinations on anesthesia quality, patient comfort, and post-anesthesia recovery in children undergoing sedation for MRI. Although there are studies comparing the midazolam-ketamine combination with different agents in the literature, to our knowledge, there has been no comparative study evaluating the midazolam-propofol combination in patients undergoing sedation for MRI. Acworth et al. and Dachs et al. suggested that the addition of midazolam to ketamine reduces the adverse effects of ketamine such as unpleasant dreams and hallucinations (Acworth et al. 2001; Dachs and Innes 1997). Therefore, we used ketamine in combination with midazolam to reduce the side effects of ketamine. Moreover, both studies also suggested that the use of propofol in MRI procedures leads to a number of side effects including reduced blood pressure and HR, apnea, and hypoventilation. Accordingly, we reduced the dose of propofol in the M-P group.

Özdamar et al. compared the use of propofol and ketamine at a dose of 1.5 mg/kg in MRI procedures. The authors indicated that the propofol group showed deeper sedation and faster awakening while the ketamine group had less cardiovascular and respiratory side effects (Özdamar et al. 2010). Moreover, Maneglia et al. showed

Table 6 SPO₂ values

	Midazolam-Ketamine	Midazolam-Propofol	<i>p</i>
Min 1	98.75 ± 1.48	98.85 ± 1.78	0.848
Min 5	98.8 ± 1.57	99.05 ± 1.23	0.58
Min 10	98.8 ± 1.23	99.3 ± 1.03	0.174
Min 15	99.25 ± 1.01	99.4 ± 1.14	0.664
Min 20	99.4 ± 0.94	99.55 ± 0.75	0.582
Min 25	99.5 ± 0.94	99.75 ± 0.55	0.313
Min 30	99.5 ± 1.00	99.85 ± 0.36	0.15

Values are expressed as mean ± SD

Table 7 Heart rate (HR) values

	Midazolam-Ketamine	Midazolam-Propofol	<i>p</i>
Min 1	119.1 ± 16.23	115.6 ± 21.87	0.569
Min 5	121 ± 15.32	114 ± 21.10	0.237
Min 10	120.8 ± 15.27	112.65 ± 20.28	0.157
Min 15	117.75 ± 15.17	111.3 ± 20.09	0.259
Min 20	117.9 ± 13.89	106 ± 20.5	0.142
Min 25	117.65 ± 12.3	106.95 ± 19.48	0.045
Min 30	117.95 ± 12.69	106.2 ± 18.9	0.027

Values are expressed as mean ± SD

that systemic vascular resistance and cardiac index increased with positive inotropic and chronotropic effects of ketamine (Maneglia and Cuosin 1988). However, propofol has been reported to reduce SBP, DBP, cardiac output, and myocardial oxygen delivery (Dachs and Innes 1997). Godambe et al. administered 1 mg/kg iv propofol in their patients and reported that propofol, due to its short duration of effect and rapid recovery, can be recommended for sedation compared to ketamine of 1-2 mg/kg iv despite its side effects such as respiratory depression and airway obstruction (Godambe et al. 2003). Another study compared the use of propofol and the midazolam-propofol combination and reported that the midazolam-propofol combination provided drug synergy and deeper and longer sedation. Additionally, the combination also improved patient satisfaction although it resulted in prolonged recovery time (Kang et al. 2017). A previous study compared the use of midazolam and propofol in children undergoing sedation for MRI. The authors found a significant decrease in DBP values in patients receiving propofol and proposed that propofol is more effective than midazolam and provides an appropriate level of sedation relatively faster (Sebe et al. 2014). Another study showed that a bolus dose of ketamine and propofol (1 mg/kg each) and propofol infusion of 50 mcg/kg/min were equally effective in terms of respiratory stability and imaging quality. The authors also noted that the administration of single-dose ketamine reduced propofol requirements and provided significantly faster recovery without increasing the incidence of anesthetic complications (Sethi et al. 2014). In another study, Bloomfield et al. reported that 97% of the patients that received propofol woke up in 1-18 min after the induction of sedation (Bloomfield et al. 1993), which was similar to that of our study. Chou et al. reported that a single dose of propofol provided appropriate sedation in children undergoing MRI procedures lasting less than 30 min (Cho et al. 2010). Similarly, in our study, a single dose was also sufficient for all the subjects.

Our results indicated no significant difference between the two groups with regard to gender, duration of MRI

procedure, and total duration of procedure. The MRI scanning quality was very good in 14 (70%) and moderately good in 6 (30%) subjects in the M-K group, whereas the scanning quality was very good in 9 (45%) and moderately good in 11 (55%) subjects in the M-P group. The MRI scanning procedure was completed uneventfully in both groups. In terms of SBP, DBP, and HR values, there were significant differences between the two groups at different times, and in the M-P group, these parameters decreased at all times compared to their baseline values. On the other hand, no significant difference was found between the groups with regard to SpO₂ values ($p = 0.826$). Moreover, no significant side effect was observed and no patient required additional sedation throughout the procedure in both groups. The groups were also similar with regard to family satisfaction and RSS scores ($p > 0.05$).

Our study was limited in several ways. First, it was a single-center study with a relatively small sample size. Secondly, despite achieving adequate sedation in both groups, the drugs were used only for the MRI procedure. Meaningfully, the dosages used in the study may be inadequate in interventional procedures. Finally, patients with an ASA status III or higher were excluded from the study, mainly because there is need for further studies for administering safe sedation in these patients.

Conclusions

Our study showed that the ketamine-midazolam and propofol-midazolam combinations provided effective sedation in children undergoing sedation for MRI. However, the ketamine-midazolam combination provided better hemodynamic stability than the midazolam-propofol combination. The wide margin of safety in ketamine and its cardiopulmonary repressive properties, as well as the absence of its anxiolytic and analgesic effects in children, make the ketamine-midazolam combination an ideal drug combination in this patient group. However, the results revealed no significant difference between the two groups in terms of patient comfort, post-anesthesia recovery, MRI scanning quality, and family satisfaction. Overall, it appears that both ketamine-midazolam and propofol-midazolam combinations meet the demands of safety and have the advantage of simplicity, rapid induction, and fast recovery; therefore, both of them can be safely used for daily anesthesia.

Abbreviations

ASA: American Society of Anesthesiologists; DBP: Diastolic blood pressure; HR: Heart rate; max: Maximum; min: Minimum; MRI: Magnetic resonance imaging; n : Number of patients; RSS: Ramsay sedation scores; SBP: Systolic blood pressure; SD: Standard deviation; SPO₂: Oxygen saturation; SPSS: Statistical Package for Social Sciences

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Authors' contributions

ÖÜ, MD, RK, AT, and ED analyzed and interpreted the patient data. ÖÜ, performed data collection and tabulation. All authors shared the writing and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by Adiyaman University Medical School Ethics Board (approval no:29.01.2015, 57831858/3), and the study was conducted in accordance with the Helsinki declaration. A written informed consent from the participants was given by their parents before the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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