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Research Article

Comparison of the efficacy of dexmedetomidine, ketamine, and a mixture of both for pediatric MRI sedation

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KEYWORDS

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Abstract *Aim:* To compare the efficacy of intramuscular ketamine, dexmedetomidine, and a mixture of both for pediatric MRI sedation.
Subjects and methods: One-hundred and sixty-two children with ASA physical I–II were enrolled in a double-blind comparative study and assigned into three equal groups for sedation. Group D, patients received IM dexmedetomidine 3 μg/kg. Group K, patients received IM ketamine 4 mg/kg. Group DK, patients received a combination of IM dexmedetomidine 1.5 μg/kg and ketamine 2 mg/kg. Primary outcomes included incidence of failed sedation and the requirement of midazolam supplementation. Secondary outcomes were time to sedation, duration of sedation, and discharge time.
Results: The onset of satisfactory sedation was significantly shorter in the DK group in comparison with the D group (4.8 ± 1.6 vs. 16.8 ± 4.5 min), while no significant difference between the DK group and K group. The duration of sedation was significantly less in the DK group in comparison with the K group, and the discharge time was significantly less in the DK group in comparison with the D and K groups. The sedation failure rate was significantly lower in the DK group (5.6%) in comparison with the K group (22.2%) and the D group (27.8%). The use of rescue midazolam was significantly less in the DK group (0.03 ± 0.12 mg) in comparison with the K and D groups (0.21 ± 0.41 mg, 0.24 ± 0.41 mg, respectively). None of the patients experienced episodes of hypotension or bradycardia in the DK and K groups while four patients (7.4%) experienced episodes of hypotension and five patients (9.3%) experienced episodes of bradycardia in the D group.

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Conclusion: In pediatric MRI sedation, the combination of IM dexmedetomidine and ketamine was superior to either IM dexmedetomidine or ketamine given individually with regard to the onset of sedation, the sedation failure rate, and hemodynamic stability.

1. Introduction

MRI scanning poses a challenge to the anesthesiologists in providing adequate sedation without compromising the patient's airway or hemodynamics and ensuring rapid recovery. The additional safety challenges posed by remote locations make the highest level of vigilance essential during MRI study when planning and performing sedation for children [1]. Dexmedetomidine has been associated with rapid onset and offset and a natural, sleep-like state [2], but patients receiving dexmedetomidine have been observed to be easily aroused by minimal stimulants, such as MRI noise. Movement was noted to be a problem by using dexmedetomidine that leads to MRI rescanning [3]. The adverse effects of alpha-2 agonist are dose-dependent [4,5]. Bradycardia and hypotension are the most reported side effects of IV dexmedetomidine [4,6–8]. The experience of concurrent use of Intramuscular (IM) dexmedetomidine with other agents in pediatric sedation is lacking. It is potential to administer the dexmedetomidine in conjunction with other agents [9] to avoid the adverse effects of dexmedetomidine. The individual disadvantages of dexmedetomidine and ketamine can be counterbalanced when used in combination [10]. The aim of the study was to compare the efficacy of intramuscular dexmedetomidine, ketamine, and a mixture of both for pediatric MRI sedation.

2. Patients and methods

One-hundred and sixty-two patients between the ages of 2–7 years with ASA physical status I–II, planned for elective MRI were enrolled in a double-blind comparative study, after obtaining approval of the hospital's Research Ethics Committee and written informed consent from parents to the study. The study was carried out from March 2010 to April 2012. Patients with a history of active upper or lower respiratory tract disease, renal or hepatic diseases, cardiovascular disease, and current use of digoxin or beta blockers were excluded. Patients with increased intracranial pressure, previous adverse reaction to ketamine or by reason of parents' refusal were also excluded from the study. Sample size was calculated using EPI-INFO program. The incidence of sedation failure was the primary endpoint of the study. The alpha-error level was fixed at 0.05 and power was set at 80% while the expected change to be detected was 10%. The required study size was 54 patients per group. Patient demographic data, patient's ASA physical status, type of MRI study performed, and its imaging time were recorded. Patients were randomized to one of three groups: Group D (n = 54) where sedation was carried out using IM dexmedetomidine hydrochloride (Precedex®, Abbott) 3 μg/kg; Group K (n = 54) where patients received IM ketamine [11] (Hikma pharmaceutical Jordan) 4 mg/kg; and Group DK (n = 54) where patients received single IM dexmedetomidine and ketamine, half the doses mentioned above for both drugs (1.5 μg/kg and 2 mg/kg, respectively). Parents were instructed to make their children NPO for solids 6 hours (h) prior to their scheduled appointment and to give clear liquids up to 2 h prior to the procedure. Before the procedure, EMLA cream was applied 1 h to the places of intravenous (IV) cannulation and IM injection. Monitoring of electrocardiogram (ECG), peripheral oxygen saturation (SPO2), and non-invasive blood pressure (NIBP) was established before the procedure. Rhythm and heart rate (HR) were displayed by using a lead II ECG. All sedatives were mixed with 0.9% saline in a syringe to a total volume of 1.5 ml by a nurse, and then, the injection was administered by blinded anesthetists to the medication. The selected sedative was given as a single IM injection in the lateral upper thigh muscle using a 25 gauge needle. Randomization was performed by means of a computer generated random-numbers table. The patients were randomly assigned on one-to-one ratio. Sedation levels were consecutively assessed with Ramsay sedation score (RSS). Primary outcomes included the incidence of failed sedation and the requirement of midazolam supplementation. Secondary outcomes were time to sedation, duration of sedation, and discharge time. Incidence of adverse events was noted.

The following data were collected by anesthesiologists blinded to the group assignment. All variables of vital signs (measured MBP, HR, SPO2, and RR) were recorded at baseline, pre-sedation, 5-min intervals throughout the procedure and every 10 min post-sedation in the recovery room. Imaging time referred to the duration of imaging study from initiation of scan till the radiologist confirms completion of successful MRI study. The time to sedation is defined as the time in minutes (min) from administration of sedative to achievement of adequate sedation (RSS 4) of the patient. Duration of sedation is defined as the time from onset of sedation to offset of sedation (RSS 2). Time to discharge is the time from giving sedation to point at which patient attained the discharge criteria (Alderete score of 8 or greater) [12]. A failed sedation refers to inadequate sedation (RSS less than 4) or inability to complete the planned procedure secondary to unacceptable motion artifacts.

The sedation was classified as failed if the sedation was deemed inadequate after 30 min, and supplemental sedation was provided by using titrated doses of IV midazolam 0.05 mg/kg every 4 min up to 0.4 mg/kg). Incidence of complications during and after the procedure was documented by the anesthetists. Hypotension and bradycardia were defined as deviation of greater than 20% below the child's baseline. Oxygen desaturations less than 92%, airway complications, emergence phenomena, vomiting, and unplanned admission were recorded. The radiologist evaluated their satisfaction of sedation "quality of MRI and continuity of MRI procedure", using a 10-cm Visual Analog Scale (VAS) score (0, sedation unsatisfactory and 10, sedation very satisfactory).

Statistical analyses: Data were analyzed using the IBM computer using SPSS version 12. The data are presented as means ± standard deviation (SD) for continuous variables and as counts and percentages for nominal data. The one

way ANOVA test for independent means, or Pearson's chi-square test where appropriate was used to identify differences between the groups. A probability value of less than 0.05 was considered statistically significant.

3. Results

There was no statistical significant difference between the groups with respect to patient's characteristics, type, and duration of the imaging studies ($p > 0.05$; Tables 1 and 2). The onset of satisfactory sedation was significantly shorter in the DK group in comparison with the D group (4.8 ± 1.6 min vs. 16.8 ± 4.5 min), while no significant difference between the DK group and K group (Table 3). The duration of sedation was significantly less in the DK group in comparison with the K group, and the discharge time was significantly less in the DK group in comparison with the D and K groups (Table 3). Although all the patients successfully completed the MRI studies, the sedation failure rate was significantly lower in the DK group (5.6%) in comparison with the K group (22.2%) and the D group (27.8%), (Table 3). Also, the use of rescue midazolam was significantly less in the DK group (0.03 ± 0.12 mg) in comparison with the K and D groups (0.21 ± 0.41 mg, 0.24 ± 0.41 mg, respectively) (Table 3). The radiologists were significantly very satisfied in the DK group regarding the quality of MRI and the continuity of MRI procedure, in comparison with the D and K groups, (Table 3). In the 5th to 45th min intervals, patients in the DK group had significantly higher HR compared to patients in the D group ($p < 0.05$) while they had significantly lower HR compared to the patients in K group ($p < 0.05$; Table 4). Also, in the 5th to 35th min intervals, patients in the DK group had significantly lower MBP compared to patients in the K group ($p < 0.05$, Table 5). Although the MBP dropped more in the D group compared with the DK group, the difference was statistically insignificant ($p > 0.05$, Table 5). During the imaging procedure, none of the patients experienced episodes of hypotension or bradycardia in the DK and K groups while four patients (7.4%) experienced episodes of hypotension and five patients (9.3%) experienced episodes of bradycardia in the D group (Table 6). On the other hand, the incidence of tachycardia and hypertension was 22.2% and 12.96%, respectively, in

Table 1 Patient demographics and clinical characteristics.

Group parameter	Group D ($n = 54$)	Group DK ($n = 54$)	Group K ($n = 54$)	Significance
Age (year)	3.78 ± 1.39	3.89 ± 1.49	3.83 ± 1.15	NS
Weight (kg)	15.31 ± 2.70	16.17 ± 3.38	15.61 ± 3.04	NS
ASA I/II	19/35	22/32	21/33	NS
F/M	28/26	27/27	27/27	NS
Imaging time	24.0 ± 3.9	24.0 ± 3.9	24.1 ± 3.6	NS

Values are expressed as mean ± SD or absolute numbers.
Abbreviation: Male, M; female, F.
NS = no significant difference; $p > 0.05$.

Table 2 Distribution of the MRI studies in the three groups.

Type of examination	Group D ($n = 54$)	Group DK ($n = 54$)	Group K ($n = 54$)	Significance
Head or neck	33 (61.1%)	33 (61.1%)	30 (55.5%)	NS
Spine	3 (5.6%)	6 (11.2%)	6 (11.2%)	NS
Thorax	6 (11.2%)	3 (5.6%)	6 (11.2%)	NS
Abdomen	9 (16.6%)	9 (16.6%)	9 (11.2%)	NS
Extremity	3 (5.6%)	3 (5.6%)	3 (5.6%)	NS

Table 3 Sedation clinical characteristics in the three groups.

Group parameter	Group D ($n = 54$)	Group DK ($n = 54$)	Group K ($n = 54$)	Significance p value
Onset of sedation	16.8 ± 4.5*	4.8 ± 1.6*	4.6 ± 1.5	0.010
Duration of sedation	25.8 ± 3.6	24.7 ± 3.1*	47.8 ± 4.5*	0.030
Time to discharge	37.2 ± 5.3*	29.9 ± 2.1*,#	54.9 ± 3.7#	0.030
Sedation failure rate	15 (27.8%)	3 (5.6%)	12 (22.2%)	0.007
Rescue midazolam	0.24 ± 0.41*	0.03 ± 0.12*,#	0.21 ± 0.41*,#	0.002
Radiologist satisfaction	7.44 ± 0.5	9.33 ± 0.5	8.17 ± 0.6	0.004

Values are expressed as mean ± SD or absolute numbers.
* $p < 0.05$: comparing DK group to D regarding the onset of sedation.
* $p < 0.05$: comparing DK group to K group regarding duration of sedation.
* $p < 0.05$: comparing DK group to D group regarding the discharge time and midazolam supplementation.
# $p < 0.05$: comparing DK group to K group regarding the discharge time and midazolam supplementation.

Table 4 Hemodynamic variables (HR) comparing the three groups.

Group intervals	Group D (n = 54)	Group DK (n = 54)	Group K (n = 54)	Significance (p value)
Baseline	100.50 ± 3.76	99.39 ± 4.02	99.17 ± 2.20	NS
5 min	85.17 ± 2.94[#]	98.56 ± 3.36[*#]	104.28 ± 4.97[*]	0.034
10 min	82.89 ± 6.92[#]	97.72 ± 3.43[*,#]	110.44 ± 10.36[*]	0.026
15 min	83.44 ± 9.28[#]	97.17 ± 3.59[*,#]	111.61 ± 8.31[*]	0.029
20 min	85.83 ± 8.71[#]	97.39 ± 3.68[*,#]	112.33 ± 6.95[*]	0.027
25 min	88.00 ± 6.42[#]	98.17 ± 3.70[*,#]	109.61 ± 6.32[*]	0.033
35 min	89.83 ± 5.38[#]	99.50 ± 3.68[*,#]	104.06 ± 4.04[*]	0.038
45 min	93.89 ± 3.91[#]	99.17 ± 3.40[#]	101.33 ± 2.93	0.040

Values are expressed as mean ± SD (M ± SD).
[*] $p < 0.05$: comparing DK group with K group at 5–35 min intervals.
[#] $p < 0.05$: comparing DK group with D group at 5–45 min intervals.

Table 5 Hemodynamic variables (MBP) comparing the three groups.

Group interval	Group D (n = 54)	Group DK (n = 54)	Group K (n = 54)	Significance p value
Baseline	62.67 ± 4.92	62.72 ± 6.33	62.83 ± 4.85	NS
5 min	61.00 ± 4.22	59.67 ± 6.21[#]	65.83 ± 4.77[#]	0.024
10 min	57.50 ± 4.15	59.50 ± 6.52[#]	67.44 ± 4.77[#]	0.015
15 min	55.22 ± 6.85	59.61 ± 6.74[#]	67.83 ± 4.63[#]	0.018
20 min	56.67 ± 5.18	59.78 ± 6.17[#]	67.56 ± 5.00[#]	0.016
25 min	57.72 ± 5.26	59.44 ± 5.97[#]	67.06 ± 5.61[#]	0.020
35 min	58.89 ± 4.80	59.56 ± 6.09[#]	65.50 ± 4.49[#]	0.022
45 min	59.94 ± 4.94	59.61 ± 6.38	63.22 ± 4.48	NS

Values are expressed as mean ± SD (M ± SD).
[#] $p < 0.05$: comparing DK group with K group at 5–35 min intervals.

Table 6 Incidence of adverse events and complications.

Group variable	Group D (n = 54)	Group DK (n = 54)	Group K (n = 54)
Bradycardia	5 (9.3%)	0 (0.0%)	0 (0.0%)
Tachycardia	0 (0.0%)	0 (0.0%)	12 (22.2%)
Hypotension	4 (7.4%)	0 (0.0%)	0 (0.0%)
Hypertension	0 (0.0%)	0 (0.0%)	7 (12.96%)
Oxygen desaturation	2 (3.7.%)	0 (0.0%)	6 (11.1%)
Vomiting	1 (1.85%)	3 (5.6%)	8 (14.8%)
Emergence phenomena	0 (0.0%)	1 (1.85%)	7 (12.96%)

the K group, while there were none in the D and DK groups (Table 6). Patients in the K group had significantly higher incidence of vomiting (14.8%) and emergence phenomena (12.96%), compared to the D and DK groups (Table 6). The incidence of peripheral oxygen desaturation events was 11.1% in the K group, 3.7% in the D group and none in the DK group (Table 6). Patients responded to head repositioning and assisted oxygen mask ventilation. Oral airway placement was required in two patients in the K group and one patient in the D group. Oral suction for secretion was required in four cases in the K group. None of the patients in the three groups required hospital admission.

4. Discussion

Dexmedetomidine may be useful for pediatric sedation in a variety of clinical situations [7]. The adverse events related to its IV administration including bradycardia, hypotension, and easy arousability by minimal stimulants such as MRI noise, presented a number of obstacles for successful sedation. On using high dose dexmedetomidine as a sole sedative for pediatric MRI, the cardiovascular side effects were noted in 16% of patients [13]. On the other hand, movement of children was noted to be a problem on using low dose of dexmedetomidine and the addition of propofol was essential for rescanning [3].

There are a limited number of studies regarding using the IM dexmedetomidine, and the experience of concurrent use of dexmedetomidine with other agents in pediatric sedation is lacking. The IM dexmedetomidine administration could be an alternative to the IV dexmedetomidine use for pediatric sedation [14]; however, the IM administration has a late sedation onset compared to the IV route [15]. The dexmedetomidine given intramuscularly reduces the sedation failure rate, the need for supplement sedation and the incidence of hemodynamic instability associated with the IV administration [15]. The mixture of dexmedetomidine and midazolam showed adequate sedation for MRI; however, the combination resulted in more cases of prolonged recovery, bradycardia, and hypotension in pediatric patients [16]. Also, 12.5% of infants and children who received IV ketamine and dexmedetomidine prior to diagnostic or therapeutic cardiac catheterization, required an earlier reduction in the infusion rate of dexmedetomidine to 1 μg/kg/h because of bradycardia and 18.5% of patients required a supplemental dose of ketamine [17]. The intramuscular mixture of dexmedetomidine and ketamine administration might avoid the adverse effects associated with dexmedetomidine and might reduce the need for titration, which is essential for IV sedation [18].

In this study, the patients given the ketamine–dexmedetomidine regimen had less sedation failure rate and required fewer rescue doses of midazolam compared with the patients given ketamine or dexmedetomidine separately. Also, patients given the ketamine–dexmedetomidine mixture required less time to be successfully sedated compared to patients given dexmedetomidine and required less time to discharge compared to patients given ketamine. Administration of an alpha-2 agonist in conjunction with ketamine as part of a balanced regimen might have a synergistic effect. This leads to improved quality of sedation [9] and reduced incidence of adverse events. A case series described the use of intravenous dexmedetomidine with ketamine for MRI in three mechanically ventilated children with trisomy 21 and obstructive sleep apnea [19]. The regimen was effective, achieving sedation to properly complete MRI, without clinically significant effects on hemodynamics or respiratory rate [19]. Also, Murat et al. [10] compared the sedo-analgesic effects of intravenous ketamine–dexmedetomidine and ketamine–midazolam on dressing changes of adult burn patients. They noted both combinations offered an effective sedo-analgesia without causing any significant side effect, but the ketamine–dexmedetomidine regimen resulted in higher sedation scores.

In this study, patients given the IM dexmedetomidine–ketamine combination showed less adverse effects and high radiologist satisfaction of sedation compared to the other sedatives. Hypotension and bradycardia are the most reported adverse effects of IV dexmedetomidine [4,6,8,9]. Dexmedetomidine has an alpha-2 agonist effect on the sympathetic ganglia [5,20], and it produces dose-dependent decreases in blood pressure and heart rate. Dexmedetomidine (2 μg/kg/h) use in children undergoing computed tomography [21] led to higher drop in blood pressure and heart rate compared with baseline. In this study, the hemodynamic status was stable without clinically significant changes in the dexmedetomidine–ketamine group; however, significant drop in MAP and HR were noted in the dexmedetomidine only group. The hemodynamic side effects of dexmedetomidine and ketamine are the opposite of each other. The dexmedetomidine provides a counterbalance to the sympathetic stimulation and attenuates the hyper-adrenergic state associated with ketamine [10,22]. The use of dexmedetomidine as a premedication was noted to be effective in attenuating the cardio-stimulatory and post-anesthetic delirium effects of ketamine [23]. Oxygen desaturation, vomiting, and emergence phenomena occurred more frequently in the ketamine group as compared to the other groups. The characteristics of ketamine and dexmedetomidine are different with respect to these outcomes. Although ketamine is not a respiratory depressant and has the advantage of maintaining protective airway reflexes [24], Owens et al. reported that 2.9% of the patients who received ketamine during sedation experienced side effects such as desaturation [25].

On the other hand, dexmedetomidine does not have active role on the respiratory system [25,26]. There were no signs of airway obstruction and hypoxemia attributed to dexmedetomidine use [27]. Vomiting is common in patients receiving ketamine. Green et al. reported the incidence of vomiting to be 3.5% in those aged less than 5 years and 12.1% in those aged 5 years or older [28]. The rate of emesis is dose related, and it was 7.0% when the total ketamine dose was 7 mg/kg or less and 11.1% when greater than 7 mg/kg [29]. On other side, nausea and vomiting are rare side effects of dexmedetomidine [8,30], and in some studies, the use of dexmedetomidine has been shown to decrease the antiemetic use [31].

IM dexmedetomidine given in combination with ketamine might have broad applications for sedation in children. The individual disadvantages of dexmedetomidine and ketamine can be counterbalanced when used in combination [10]. Although the concurrent use of dexmedetomidine and ketamine might be useful regarding the quality of sedation, different doses of intramuscular dexmedetomidine–ketamine mixture need to be compared to determine the optimal regimen for pediatric sedation.

5. Conclusion

In pediatric MRI sedation, the combination of IM dexmedetomidine and ketamine was superior to either IM dexmedetomidine or ketamine given individually with regard to the onset of sedation, the sedation failure rate, and hemodynamic stability.

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