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Research Article

A Comparative Study of the Effect of Dexmedetomidine-Fentanyl and Midazolam-Ketamine Combination on the Level of Sedation in Children undergoing Bone Marrow Biopsy

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ABSTRACT

Background: This study aimed to compare the effect of dexmedetomidine-fentanyl (DF) and midazolam-ketamine (MK) combination on the level of sedation in children undergoing bone marrow biopsy.

Methods: This study was a single-blind randomized clinical trial. The patients were divided into two groups of 35. Five minutes before undergoing bone marrow biopsy, the first group underwent sedation with a combination of 0.1 mg/kg midazolam with 1 mg/kg ketamine, and the second group underwent sedation with a combination of 2 µg/kg dexmedetomidine with 1 µg/kg fentanyl. The mean arterial pressure (MAP), heart rate, SpO2, the level of sedation, and the incidence rates of complications were recorded in both groups and compared to each other.

Results: There was no significant difference between the two groups in terms of age (P= 0.687), gender (P= 1.00), and weight (P= 0.839). However, there was a significant difference in the average length of stay in recovery (P= 0.015) and surgeon satisfaction (P= 0.000), with a longer recovery period in the midazolam-ketamine (MK) group. The Repeated measures ANOVA showed significant differences in heart rate (P= 0.008), sedation score (P= 0.038), and the percentage of oxygen saturation (P= 0.00) during surgery.

Conclusion: The combination of dexmedetomidine and fentanyl (DF) compared to the combination of midazolam and ketamine (MK) can provide more patient sedation and surgeon satisfaction along with more stable hemodynamics for patients undergoing bone marrow biopsy.

Nowadays, invasive measures such as Bone Marrow Aspiration (BMA) & Biopsy are regarded as an integral part of diagnostic and therapeutic procedures in children with blood malignancies. These measures are painful and often difficult to tolerate, thus resulting in great anxiety in this group of children and their parents [1]. Furthermore, these methods may lead to other mental health problems in children as well [2]. The World Health Organization (WHO) and the American Academy of Pediatrics (AAP) recommend general anesthesia or the use of a combination of analgesics for these painful diagnostic and therapeutic procedures in children [3]. Various approaches to control anxiety and pain such as educating parents and children, cognitive behavior therapy (CBT), general anesthesia, and palliative medicine have been proposed. General anesthesia is associated with respiratory, cardiovascular, and neuromuscular depression. Patients require using mechanical ventilation during general anesthesia [4].

Midazolam is a short-acting water-soluble benzodiazepine with quick action and high lipophilicity. Its pharmacological properties include sedation, anti-anxiety, anterograde amnesia, anticonvulsant,

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cardiovascular stability, and muscle relaxation [5]. However, this drug causes some side effects such as postoperative behavioral changes, cognitive impairment, paradoxical reactions, and respiratory depression [5-7].

Ketamine is a derivative of phencyclidine which possesses sedative and analgesic properties. It can be used alone or in combination with other drugs to provide analgesia during diagnostic and therapeutic procedures in children. It is excellent in terms of safety and associated with the maintenance of spontaneous respiration and airway reflexes [8]. Postoperative nausea and vomiting are common. Saliva increases after taking the drug [9].

Another proposed drug is dexmedetomidine, a selective alpha-2 adrenoceptor agonist. The drug can be used as an adjuvant in general anesthesia, which in turn exerts central sympatholytic effects, contributes to providing a stable hemodynamic status for patients, and also exerts an excellent sedative effect without respiratory depression, which reduces the need to take opioids and subsequent complications and also decreases stress response, improves the quality of recovery, and causes a mild cognitive impairment (MCI), leading to establishing easy communication between the medical team and the patient in the intensive care unit (ICU) as well as in cases requiring monitoring [10].

Fentanyl is a potent opioid agonist with a rapid onset of action and short duration of action. Its advantages over other analgesics include the lack of histamine release and sustained cardiovascular effects [11]. Respiratory depression is the most common side effect of the drug, which is often dose-related [12].

Even though lots of research has been conducted on different methods of sedation in children, there is still no combination that is agreed upon by all experts. Given that there have been no studies regarding comparing the effect of the combination of dexmedetomidine-fentanyl (DF) versus midazolam-ketamine (MK) on the sedation level of children undergoing bone marrow biopsy, we decided to carry out the present study.

Methods

This study was a single-blind randomized clinical trial conducted on children aged 2 to 6 years who were candidates for bone marrow biopsy in 2020 in Mofid Children's Hospital of Shahid Beheshti University of Medical Sciences after receiving the written consent of the children's parents, gaining proposal approval, obtaining permission from the Medical Ethics Committee of the University of Medical Sciences (code: IR.SBMU.RETECH.REC.1399.138), and after the trial was registered in the Iranian Registry of Clinical Trials (code: IRCT20160301026866N11). Samples were selected using stratified block randomization. Considering the sedation score in the study by Gelen SA et al. as well as the test power of 80%, the significance level of 95%, and the error of 5% ($\alpha = 0.05$), the intended sample size was determined to be 35 for each group and 70 in total.

Inclusion criteria included children aged 2 to 6 years with ASA I and ASA II class, who were candidates for bone marrow biopsy. Exclusion criteria included the presence of congenital heart and respiratory diseases, productive cough, fever, wheezing or crackling in the lungs, and the parents' withdrawal from participation in the research design.

The checklist used in this study was a researcher-made checklist that included heart rate, mean arterial pressure (MAP), SpO2, and level of sedation based on the Ramsay scale. This information was recorded immediately before drug administration and 2, 5, 10, and 15 minutes after drug administration. Patients were divided into two groups through stratified block randomization. The first group underwent sedation with 0.1 mg/kg midazolam plus 1 mg/kg intravenous (IV) ketamine. The second group underwent sedation with 1 μg/kg fentanyl plus 2 μg/kg intravenous (IV) dexmedetomidine. Immediately after receiving the drug, patients received oxygen via a cannula. Two minutes after the drug was administered and after ensuring that patients received adequate sedation (Ramsay score of 4 or higher), the pediatrician was allowed to perform the procedure. Then, the information mentioned for 15 minutes after drug administration was recorded, and according to the Modified Aldrete Score criterion, the length of stay in recovery was recorded in both groups and compared to each other. According to the 5-point Likert scale, the satisfaction of the pediatrician performing the procedure was recorded in both groups and compared to each other. After the drug was administered, the incidence rates of any complications including tachycardia (heart rate greater than 20% of baseline), bradycardia (heart rate less than 20% of baseline), increase or decrease of mean arterial pressure (MAP) (changes of more than 20% of baseline mean arterial pressure), apnea, arterial oxygen saturation drop below 90%, cough, laryngospasm, and bronchospasm were recorded in both groups and compared to each other. The method of blinding was such that patients and the data recorder were unaware of group assignment.

Eventually, after the data were collected, they were entered into SPSS software version 23. In this regard, the percentage frequency was used to describe the qualitative variables, and mean ± standard deviation (SD) was used to describe the quantitative variables. To measure the differences between the two groups, the statistical tests such as T-test and chi-square were used, and to evaluate the effect of the two drug combinations, the repeated measures analysis was used.

Results

Table 1 compares the mean and frequency distribution of demographic variables, satisfaction score, and length of stay in recovery between the two groups. There was no significant difference in the mean age and weight

variables between the two groups. Also, the frequency distribution of gender in both groups was equal ($p > 0.05$). However, the results showed that there was a significant difference between the two groups in terms of length of stay in recovery and the pediatrician satisfaction score ($p < 0.01$). Evaluating the frequency pattern of the pediatrician satisfaction score showed that the highest pediatrician satisfaction was in the DF group and the shortest length of stay in recovery was also in the same group. Although higher incidence rates of complications such as apnea, laryngospasm, bronchospasm, SpO2 drop, and HR drop below 20% were reported in the MK group, the difference was not statistically significant ($P = 0.428$).

The results obtained from the evaluation of hemodynamic parameters in both groups before drug administration and 2, 5, 10, and 15 minutes after drug administration are presented in Table 2. According to the Repeated measures ANOVA, there was a significant difference in heart rate, the percentage of oxygen saturation, and sedation score between the two groups ($pgroup< 0.05$), and only the Mean arterial pressure (MAP) did not differ significantly between the two groups ($pgroup > 0.05$). As shown in Table 2, among the study groups, the DM group had a significantly lower mean heart rate (MHR) than the MK group. As presented in Table 2, the MAP in the DF group was also lower than in the MK group, although the difference was not statistically significant. According to the results given in Table 2, the sedation score was higher in the MK group and the mean percentage of oxygen saturation was significantly lower in the MK group.

On the other hand, the evaluation of hemodynamic parameters in both groups before drug administration and 2, 5, 10, and 15 minutes after drug administration showed a significant difference during this time ($ptime < 0.05$). Meanwhile, only the MAP in the DF group did not change significantly over time ($ptime > 0.05$) (Table 2).

Table 1- Comparison of demographic characteristics, length of stay in recovery, and satisfaction score in both groups

Variable		group Dexmedetomidine-fentanyl (DF) (N = 35)	 Midazolam-ketamine (MK) (N = 35)	P value	T statistics or chi-square
Age (years) (Mean ± SD)		3.69 ± 1.49	3.83 ± 1.46	0.687	0.404
Weight (kg) (Mean ± SD)		13.94 ± 2.40	14.06 ± 2.28	0.839	0.204
Length of stay in recovery (minutes) (Mean ± SD)		26.14 ± 6.42	30.14 ± 6.91	0.015	2.50
Side effects	No	33 (94.3%)	30 (85.7%)		
(%) Frequency	Yes	2 (5.7%)	5 (14.3%)	0.428	1.42
Gender (%)	Boy	17 (48.6%)	16 (45.7%)		
Frequency	Girl	18 (51.4%)	19 (54.3%)	1.00	1.884
Satisfaction	4	5 (14.3%)	21 (60%)		
score (%)	5	30 (85.7%)	14 (40%)	0.000	15.64
Frequency					

Table 2- Comparison of heart rate, mean arterial pressure (MAP), percentage of oxygen saturation and sedation score at different times of drug administration in both groups

Variable	Time	group Dexmedetomidine-fentanyl (D-F) (N = 35)	 Midazolam-ketamine (MK) (N = 35)	P valuegroup*
Heart rate (beat/min)	Immediately before drug administration	116.69 ± 8.50	116.51 ± 8.53	0.008
	2 minutes after drug administration	114.51 ± 8.26	120.40 ± 8.31	
	5 minutes after drug administration	113.43 ± 7.76	118.69 ± 20.26	
	10 minutes after drug administration	113.77 ± 7.87	122.17 ± 8.01	
	15 minutes after drug administration	113.57 ± 7.65	121.97 ± 7.55	
P valuetime		0.001	0.000	
Mean arterial pressure (MAP)	Immediately before drug administration	55.69 ± 4.33	55.91 ± 4.39	0.074

(mm Hg)	2 minutes after drug administration	55.71 ± 4.24	58.26 ± 4.03	
	5 minutes after drug administration	55.91 ± 4.43	59.09 ± 3.97	
	10 minutes after drug administration	56.17 ± 4.27	59.14 ± 3.85	
	15 minutes after drug administration	56.37 ± 4.34	57.03 ± 9.74	
p-valuetime		0.078	0.024	
Percentage of oxygen saturation (%)	Immediately before drug administration	98.89 ± 1.20	98.69 ± 1.36	0.000
	2 minutes after drug administration	98.49 ± 1.72	96.60 ± 2.32	
	5 minutes after drug administration	98.26 ± 2.17	95.80 ± 2.73	
	10 minutes after drug administration	98.14 ± 2.18	95.89 ± 2.69	
	15 minutes after drug administration	98.43 ± 1.63	96.54 ± 2.21	
p-valuetime		0.044	0.000	
Sedation score	Immediately before drug administration	1.80 ± 0.40	1.80 ± 0.40	0.038
	2 minutes after drug administration	4.91 ± 0.28	4.54 ± 0.23	
	5 minutes after drug administration	5.27 ± 0.38	5.07 ± 0.38	
	10 minutes after drug administration	4.83 ± 0.38	4.89 ± 0.32	
	15 minutes after drug administration	3.34 ± 0.76	3.80 ± 0.63	
P valuetime		0.000	0.000	

*By modifying the effect of the variable at the time of entering the recovery

Discussion

In this study, the Ramsay Sedation scale was used to measure the sedation level of patients since it is one of the rare sedation scales with documented reliability. Studies have shown that pre-intervention regimens, which have both the anti-anxiety effect of midazolam and the analgesic property of ketamine, lead to better behavior in children compared to taking these medications alone [13-14]. Hemodynamic parameters, i.e. heart rate and SpO2, were relatively stable in both groups during the treatment period; however, the DF group was more stable than the MK group. In a 2016 study by Abdolkarimi et al. on comparing intravenous (IV) ketamine and pethidine for bone marrow biopsy and aspiration among 57 children with malignancy, it was found that in addition to providing more hemodynamic stability, IV ketamine exerted greater clinical effects on pain relief as well [15].

The heart rate in the DF group was closer to normal and under control, whereas the heart rate in the MK group was significantly higher. Moreover, the level of SpO2 in this group was higher than 90% in all treatment procedures. There was a significant difference in the mean sedation score between the DF and MK groups; however, the level of sedation was significantly higher in the DF group than in the MK group. While in a study by Gelen SA on 115 hematology patients undergoing minor painful surgeries in 2015 in Turkey, the combination of midazolam and ketamine was evaluated and the success rate of sedation (Ramsay Score> 5) was reported to be higher than 92%. Although there was an increase in heart rate, systolic blood pressure, and respiration rate in these patients, these increases were not statistically significant [16].

Furthermore, in a series of studies regarding dental patients, it was demonstrated that the highest sedation score was associated with the MK combination, with more than 94% in one study [17], 93.3% in Norambuena et al.'s study [18], 79.3% in Darlong et al.'s study [19], 75% in Malhotra et al.'s study [20], and 97.96%. in Ghhai et al.'s study [21]. This difference in the success rates of sedation in different combinations can be attributed to different scales used for evaluation, different drug doses, different criteria used for measuring success as well as the type of disease; since in our study, a score of 4 was considered as a criterion for successful sedation, whereas in many studies, ≥ 3 was considered as a criterion. Moreover, the results obtained from the present study showed that although the mean arterial pressure (MAP)

in the MK group was higher than in the DF group, the difference was not statistically significant.

Conclusion

This study revealed that both MK and DF combination led to comparable sedation and satisfaction among children and surgeons and that the DF combination could be selected as an alternative in improving the sedation of children undergoing bone marrow biopsy. Regarding the success rate of this drug combination during treatment procedures as well as its anti-anxiety property, it looks particularly promising to children.

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