RESEARCH ARTICLE

Effect of Ketamine-Sufentanil and Ketamine-Midazolam to induce sedation and analgesia in Pediatric with Lumbar Puncture or Bone Marrow Aspiration

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Background: The combination of sedative and analgesic drugs has a favorable effect on pain management and sedation during painful procedures in pediatrics. Therefore, our aim was to compare the effect of sedation and analgesia of ketamine-sufentanil and ketamine-midazolam in painful procedures in children with blood malignancies.

Methods: This double-blind, clinical trial was performed on 82 children with malignancy who had indication of painful diagnostic intervention; patients were randomly divided into two groups of ketamine-sufentanil (KS) and ketamine -midazolam (KM).

In KS group, sufentanil 0.5mcg/ kg and ketamine 1mg/ kg and in the KM group, ketamine 1mg/ kg, and midazolam 0.1mg/ kg bolus were prescribed. In either group, hemodynamic indicators of sedation, side effects, duration of effectiveness were recorded. Data were analyzed using SPSS 20.

Results: Sedation based on Ramsay sedation score was not significantly different between the two groups (p= 0.39). The average recovery time in the midazolam-ketamine group was higher (p-value= 0.076).

Conclusion: The combination of ketamine-sufentanil and ketamine-midazolam was effective in sedation and analgesia in bone marrow aspiration and lumber puncture; side effects were however, lower in ketamine-midazolam group.

Keywords: ketamine; sufentanil; midazolam; pediatric

Lumbar puncture (LP), bone marrow aspiration or bone marrow biopsy (BMB/ BMA) is performed regularly in children with hematologic malignancies, causing pain and anxiety in these children and their parents [1-2]. Proper management of anxiety and pain is crucial since anxiety and pain may reduce the tolerance of the treatment and lead to depression or long-term physiological disorders [3-4]. At the moment, various strategies have been proposed to reduce the pain during aggressive interventions in this group of patients. These strategies include effective parenting, child preparation, cognitive-behavioral therapy, sedative medication and general anesthetic [5]. It is recommended by the World Health Organization (WHO) and the American Academy of Pediatrics (AAP) to combine sedative and analgesic medications during painful actions in children with hematologic diseases [6-8]. Currently, various drugs such as propofol, ketamine, fentanyl, alfentanil, remifentanil, midazolam or a combination, are used to induce analgesia and sedation in children [9-10]. An ideal sedative has rapid onset of effect and can provide adequate cardiovascular and respiratory function, amnesia and inactivity [11]. Unfortunately, an agent with above-mentioned features is unavailable, and therefore a combination of different agents is administered to achieve these goals [12]. In recent studies, co-administration of ketamine with midazolam and sufentanil has been suggested due to shorter recovery times and less side effects [13-15]. The aim of this study was to compare the effect of two compounds of Ketamine-Suffentanil and Midazolam on anesthetic anesthesia during painful procedures in pediatric oncology patients.

Methods

This study was a randomized, double-blind, clinical trial on 76 children aged between 1 and 14 years with hematologic malignancies who were scheduled for LP or BMA/BMB.

Exclusion criteria were history of allergy or allergic reaction to any of medication, head injury, high intraocular or intracranial pressure, cardiovascular disease, respiratory disease, liver disease, epilepsy or history of seizure, neurological disorder, tumor or metastasis of the brain, the use of any analgesic and anesthetic agent.

Intravenous ketamine (1 mg/ kg) and sulfentanil (0.5mcg/ kg) were gradually injected In KS group; in KM group, ketamine (1mg/ kg) and midazolam (0.1mg/ kg). Nasal oxygen was administered for patients. Monitoring included heart rate, respiratory rate, oxygen saturation, and non-invasive measurement of blood pressure. During the procedure, the patient's pain intensity was recorded with VAS (Visual Analogue Scale) (score from zero to 10);

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sedation level was also recorded by UMSS (University of Michigan Sedation Scale) [16]. The total duration of sedation, procedure, and recovery, and possible complications of the patient during intervention and recovery process (e.g. hypoxia, cough, bradycardia, restlessness, dizziness, nausea, vomiting, double vision, chills, illusions, and etc.) was recporded; also, need for assisted ventilation was recorded during the process. Patients were also evaluated for apnea (lack of respiration for more than 20 seconds or oxygen saturation below 90%). When the patients reached Alderete Score 9 or 10, they were discharged of recovery. Patients were monitored for at least two hours after completion of the work.

Statistical Analysis

All data were analyzed in SPSS 24.0. Chi-square, independent t-test and Mann-Whitney were used to determine the difference between the two groups; repeated measure ANOVA was used to compare changes in the results. P-values less than 0.05, were considered significant.

Results

A total of 76 children were enrolled in this study with 38 children in each group. Normality of data was confirmed by Kolmogrov Smirnov test. Data were presented as mean ± standard deviation (M±SD). The analyses showed that demographic characteristics (number, age, sex and body weight) were similar in both groups and there was no significant difference between the two groups (Table 1). The mean duration of operation in the two groups was not significantly different (p=.090); mean recovery time was higher in the MK group; this difference was not significant (p=.076). The average recovery time in MK and SK was 45.4 minutes and 42.2 minutes, respectively. Tachycardia was detected in two patients (5%) in the SK group compared to none in the MK group. Three patients (7%) in the MK group experienced increased blood pressure, compared to none in the SK group. Hypoxia was detected in 4 patients (11%) in the SK group and 1 patient (3%) in the MK group. A patient in the SK group experienced nausea and vomiting. The mean of Ramsay sedation score was similar in both groups (p=.39) (Table 2). The hemodynamic data (spO2, HR, SBP, DBP and MAP) were similar in both groups (Table 3). The observed VAS for pain during the procedure was 1.58± 1.15, in the first group and 1.63 (± 1.05) in group 2 (p= 0.009, 28.9% of the MK group and 21.1% of the SK group during the procedure. In addition, in 15.8% of the MK group and 15.8% of the SK group, they had to repeat the dosage of drugs during the procedure (P = 0.427 and P = 1.000), respectively (p=.246). However, there was no significant difference between the two groups in terms of the need for repeated dosing, for each patient, the total relaxation time, the duration of the procedure and the length of stay in the recovery, the complications of the patient during the procedure and during Recovery (including hypoxia, bradycardia, dizziness, nausea, vomiting, dizziness, chills, hallucinations, etc.), as well as the patient's need for assisted ventilation. Patients were evaluated for apnea (for breathing more than 20 seconds or decreased oxygen saturation below 90%). When modified Alderete score reached 9 to 10 the patient was discharged from recovery. Patients were monitored for at least 2 hours after surgery.

Table 1- Demographic data

Means of	MK	SK	P-value	Test
Age(yr)	6.7±3.7	6.3±2.2	0.63	T- test
Sex (M/F)	(27/11)	(26/12)	0.80	Fisher's exact
Body weight(kg)	21.1±10	20.57±7.3	0.77	T- test
Procedure				
IT	19 (50.0%)	11 (28.9%)		
BMA	5 (13.2%)	12 (31.6%)		
BMA/IT	6 (15.8%)	14 (36.8%)	0.018	Pearson Chi-Square
BMA/BMB	8 (21%)	1 (2.6%)		

Table 2- Ramsay sedation score.

Score	UMSS	Frequency (%)		P-value	Test
		MK	SK		
0	Awake and alert	0	0	---	---
1	Minimally sedated/sleepy	0	0	----	---
2	Moderately sedated	1	0	0.39	Fisher, s exact
3	Deeply sedated	9	6	0.39	Fisher, s exact
4	Unarousable	28	32	0.39	Fisher, s exact

Table 3- Patients vital signs

Means of	Time	MK	SK	p-value	Test
HR(bpm)	T0	107.4	109.7	0.605	T- test
	T1	106.5	112.7	0.108	
	T2	103.9	104.7	0.848	
SPO2(%)	T0	97.9	98.0	0.614	T- test
	T1	99.5	99.7	0.308	
		99.3	99.3	1.000	
SBP(mmHg)	T0	118.5	112.6	0.249	T- test
	T1	117.4	114.2	0.350	
	T2	107.6	111.6	0.233	
DBP(mmHg)	T0	76.5	75.1	0.698	T- test
	T1	79.5	75.5	0.273	
	T2	68.2	72.5	0.220	
MAP	T0	92.9	92.0	0.790	T- test
	T1	95.4	92.2	0.356	
	T2	84.8	88.1	0.355	
Movement	Yes	27(71.1%)	30(78.9%)	0.427	Fisher's exact
	No				
Need to repeat dose	Yes	11(28.9%)	8(21.1%)	1.000	Fisher's exact
	No				
UMSS (mean)		3.71	3.84	0.246	Mann-Whitney

T0: Indicates time before procedure, T1: Indicates Recovery, T2: Indicates time after procedure

HR: heart rate, SPO2: oxygen saturation, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP mean arterial pressure, UMSS: University of Michigan Sedation Scale.

Discussion

In this study, the two groups were similar in HR, 2SPO, SBP, DBP, MAP, and the need for repeat dose. In a study by Sajedi et al, midazolam, co-administered with ketamine, was safe and effective in controlling pain in patients [13-15]. However, various studies have shown that the combination of ketamine and fentanyl, in contrast to fentanyl alone, increases the anti-nociceptive effect of fentanyl and reduces the side effects [16]. Preoperative fentanyl administration induces repeated coughs, which may interfere with intubation and anesthesia, but administration of a small dose of ketamine a minute before the fentanyl can reduce coughs [17]. In a randomized trial by Monsereenusorn et al. on 55 children undergoing painful procedures (intrathecal chemotherapy, bone marrow aspiration and biopsy) fentanyl has a larger impact on reduction of pain and nausea, compared to ketamine [18], which is in accordance with the current study.

The present study shows that combination of ketamine and sufentanil increases effects of both drugs, in terms of hemodynamic stability during intubation and pain relief after the surgery, while side-effects of the two agents, such as nausea, vomiting and muscle stiffness and respiratory do not accumulate and may even decrease [19].

The results of the present study and previous literature show that combination of ketamine with agents like sufentanil or midazolam may be safe and effective in painful pediatric procedures. Also, this study is the first report of comparing ketamine-sufentanil and ketamine-midazolam combinations to reduce the severity of pain in painful procedures in children with hematologic malignancies.

Conclusion

Combination of ketamine with agents like sufentanil or midazolam may be safe and effective in painful pediatric procedures.

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