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

Hamidreza Shetabi¹, Amir Shafa¹*, Mohamadmehdi Zare²

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 lumbar puncture; side effects were however, lower in ketamine-midazolam group.

Keywords: ketamine; sufentanil; midazolam; pediatric
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 recorded; 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=0.090); mean recovery time was higher in the MK group; this difference was not significant (p=0.076). 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

<table>
<thead>
<tr>
<th>Means of</th>
<th>MK</th>
<th>SK</th>
<th>P-value</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(yr)</td>
<td>6.7±3.7</td>
<td>6.3±2.2</td>
<td>0.63</td>
<td>T- test</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>(27/11)</td>
<td>(26/12)</td>
<td>0.80</td>
<td>Fisher’s exact</td>
</tr>
<tr>
<td>Body weight[kg]</td>
<td>21.1±10</td>
<td>20.5±7.3</td>
<td>0.77</td>
<td>T- test</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>19 (50.0%)</td>
<td>11 (28.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMA</td>
<td>5 (13.2%)</td>
<td>12 (31.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMA/IT</td>
<td>6 (15.8%)</td>
<td>14 (36.8%)</td>
<td>0.018</td>
<td>Pearson Chi-Square</td>
</tr>
<tr>
<td>BMA/BMB</td>
<td>8 (21%)</td>
<td>1 (2.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2- Ramsay sedation score.

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

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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.

References

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1. Shetabi et al.