



Comparison Effect of Intravenous Ketamine with Sufentanil for Pain Relief during Painful Procedures in Children with Leukemia

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ABSTRACT

Background: Children with leukemia would go through different diagnostic and therapeutic procedures during their process of their disease, including lumbar puncture and bone marrow aspiration; these procedures are usually associated with pain and stress. The aim of the present study was to compare the effect of two combinations of Propofol-Ketamine and Propofol-Sufentanil on sedation and analgesia during painful procedures in children with acute lymphoblastic leukemia.

Methods: In a randomized, double-blind clinical trial, 70 children with acute lymphoblastic leukemia undergoing painful procedures were randomly allocated into two parallel groups and took Intravenous Ketamine (1 mg/kg/dose) or Sufentanil (0.5 mcg/kg/dose). Both groups received Intravenous propofol (1.2mg/kg). Hemodynamic variables and analgesic effect were compared between groups.

Results: There was no significant difference between the two groups in terms of the changes in vital signs at the time before, during and after the procedure. But, the incidence of patient's movements and the need for repeated propofol boluses was significantly lower in the Ketamine group compared to the Sufentanil group (P: 0.008).

Conclusion: Ketamine is a good choice for conducting painful procedures on children with acute lymphoblastic leukemia. Ketamine might be a good option for pain relief during painful procedures such as intrathecal injection, bone marrow aspiration. Ketamine could also be more effective in controlling the movements and decreasing the need for repeating the drug dosage compared to the Sufentanil.

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Introduction

Various procedures such as lumbar puncture and bone marrow aspiration for children with acute lymphoblastic leukemia are associated with pain and anxiety for the patients and their parents (1, 2). Minimizing the pain and mental complications caused by these interventions is one of the ideal goals of pediatric oncologists. Also

to manage the pain and anxiety, interventional methods, including medical and non-medical methods are required (3, 4). Acupuncture, creating distractions and hypnotism are some of the non-medicinal interventions for relieving the pain during the procedure or discomfort and anxiety in children with cancer (5). Using a combination of sedative and analgesic drugs during painful procedures in children with acute lymphoblastic leukemia has been recommended by the World Health Organization (WHO) and American Academy of Pediatrics (AAP) (6-8). Propofol, Ketamine, Fentanyl, Alfentanil, Remifentanil, and Midazolam are some of the drugs that are used for

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achieving sedation and analgesia in pediatric patients (9, 10). To achieve better and more appropriate effects, the drug must have rapid effect and onset, appropriate recovery and sedation period, more analgesic effects and also appropriate efficiency on the cardiovascular, respiratory and amnesia performances (1).

Unfortunately, no specific drug exists on which contain all of these characteristics at the same time; so anesthesiologists should combine different drugs with different doses to achieve this goal (11). Some studies have recommended the combination of Propofol and Ketamine as a safe and effective sedative with little side effects and rapid recovery (12, 13). Also, no study has compared the sedative and analgesic effects of Propofol-Ketamine and Propofol-Sufentanil combinations in children with acute lymphoblastic leukemia undergoing painful procedures.

Propofol, a popular sedative, fast-acting short-acting non-opioid, and non-barbiturates for routine sedation, it has anti-nausea effects and easily relaxes (14). Its side effects include the dose depended respiratory and cardiovascular suppression, Propofol is known to be an anti-nausea medicine, but has no analgesic effect, and is usually used with an analgesic drug (14-16).

Ketamine is a fast dissociative anesthetic medication that has a deep analgesic effect. Ketamine may have little or no respiratory or cardiovascular suppression effects, due to its cardiac stimulatory effects and good safety, are suitable for sedation and children (17). However, with increasing doses, it may be accompanied by some problems, such as the occurrence of emergency reactions including nightmares or alive illusions (14).

The high solubility of Sufentanil, causes analgesia and comfort during operation, Sufentanil has a short delay in onset time (5 to 10 minutes) and up to 7 hours' duration of the activity (18-20)

So the aim of the present study was to compare the effect of Ketamine and Sufentanil in pain relief in children with acute lymphoblastic leukemia undergoing painful procedures.

Methods

This is a randomized, double-blind clinical trial conducted in the pediatric hematology/oncology department of Omid Hospital, an academic oncology center affiliated to Isfahan University of Medical Sciences. This research was conducted during 2017. It was approved by the Ethics Committee of Isfahan University of Medical Sciences. The study was registered in the Iranian registry of clinical trials (registration code IRCT20170808035601N9). Written informed consent was obtained from all the patients, according to the Declaration of Helsinki.

All pediatric patients 1 to 14 years old with acute lymphoblastic leukemia who referred to the oncology

department and needed bone marrow aspiration/biopsy (BMA/ BMB) or intrathecal injection (IT) were included in the study. The exclusion criteria were history of recent head trauma, neurological disorders such as high intraocular (IOP) or intracranial Pressure (ICP), Severe or uncontrolled cardiovascular, pulmonary or liver disease, seizures, neurologic disorders, thyroid dysfunction, brain tumor or metastasis, consumption of analgesic or sedative drugs, suffering from chronic pain syndrome, unwillingness to participate in the study and a history of allergy to eggs and soy or allergic reaction to Propofol or other studied drugs. Also, patients who would develop any complications (medical allergy, seizure, etc.) during the study which led to changes in their anesthesiology plans were excluded from the study.

A double-blind randomization was done in this study. Before patients undergoing the procedure using computer-generated sequences, the patients were randomly allocated into two groups. In this study, both the participants and the data collector were blind to the allocation of the participants into ketamine and sufentanil groups.

The drugs in the two groups were the same in terms of color and volume. The study drugs were prepared by an anesthesiologist who was not involved in data collection.

Fasting duration for children younger than 6 months was 6 hours and for older children 8 hours. Patients were allowed to drink water until 2 hours prior to the surgery. In the operating room, all patients received standard monitoring included electrocardiogram (ECG), noninvasive arterial Blood pressure (NIBP), pulse oximetry (SpO₂), and end tidal carbon dioxide (EtCO₂).

Supplemental oxygen was delivered at 2 l/min through nasal cannula. Any respiratory depression, and SpO₂ of < 90% or the lack of respiratory effort for more than 10 seconds, jaw-thrust maneuver and respiratory support was performed using a face mask and air bag.

Respiratory rate, heart rate, systolic and diastolic blood pressure, average arterial pressure and oxygen saturation were measured and recorded at three different times (before the surgery, during the surgery and in the recovery room). The care for children before, during and after sedation were performed based on the recommendations of the World Health Organization and American Academy of Pediatrics (AAP) (13, 14).

Patients based on grouping received intravenous ketamine 1mg/kg/dose or Sufentanil 0.5mcg/kg/dose for pain relief. After two minutes, propofol 1.2 mg/kg in a concentration of 0.5mg/ml was injected within 30 seconds until reaching to the proper sedation level.

After the patient became unresponsive, the intervention was performed by the pediatric hematologist. In the case of occurrence of any movements during sedation, which interfered with the intervention, rescue doses (0.2 cc/kg) of propofol were administered and the total used dosage was recorded.

Table 1. Demographic and clinical characteristics of the patients of both groups.

| Characteristic | | Propofol-Ketamine group | Propofol-Sufentanil group | P value |
|-------------------------------------|----------|-------------------------|---------------------------|---------|
| Number | | 35 | 35 | - |
| Gender | Boy | 22 (62.9%) | 21 (60%) | 0.80* |
| | Girl | 13 (37.1%) | 14 (40%) | |
| Age (Mean ± SD) (years) | | 7.47 ± 3.22 | 6.24 ± 3.42 | 0.70** |
| Weight (mean ± SD) (kg) | | 26.37 ± 13.22 | 21.20 ± 11.74 | 0.27** |
| Sedation level based on UMSS | 2 | 15 (45.5%) | 20 (60.6%) | 0.46* |
| | 3 | 12 (36.4%) | 9 (27.3%) | |
| | 4 | 6 (18.2%) | 4 (12.1%) | |
| Pain intensity based on UPAT | No pain | 6 (18.2%) | 0 | 0.03* |
| | Mild | 26 (78.8%) | 32 (94.1%) | |
| | Moderate | 1 (3%) | 2 (5.9%) | |

* Chi-square test, ** Independent t-test, UMSS: University of Michigan Sedation Scale, UPAT: universal pain assessment tool

All of the sedation and analgesia stages were performed under the supervision of an anesthesiologist.

After administrating the medications, the quality of patients was evaluated using University of Michigan Sedation Scale (UMSS) (21) the depth of sedation was divided into five levels based on the Sedation Scale. Level 0: Awake and alert, Level 1: Minimally sedated: tired/sleepy, appropriate response to verbal conversation, and/or sound. Level 2: Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command. Level 3: Deeply sedated: deep sleep, aroused only with significant Physical stimulation. Level 4: Unarousable. If the patient showed a UMSS score 3 and at the beginning of the intervention, there was no movement, patient considered as successful sedation. If the child showed a score <3, required a titrated additional dose of propofol to deepen the sedation

Pain severity is categorized from 0 to 10 based on using Universal Pain Assessment Tool (UPAT)(22), it is a scoring system to assess the intensity of pain which divides the intensity to three categories of mild (scores of 1-3), moderate (scores of 4-6) and severe (scores of higher than 6) .

Blood pressure, heart rate, respiratory rate and oxygen saturation were measured before initiating sedation, every 5 minutes during the intervention and every 10 minutes in the recovery room. The onset effect times of the drug, duration of operation, duration of stay in the recovery room were measured.

If patients during the intervention experienced an arterial oxygen saturation decrease (<90%) First, the jaw thrust maneuver and then the bag-mask ventilation

(BMV) was used and the event recorded. At the end of the procedure, patients were transferred to the recovery room, monitored and after reaching an Alderete score of 9-10 were transferred to the ward. Patients were monitored for at least 2 hours after the procedure.

Analgesic effect was as the primary Outcomes of the study and side effects such as changes in blood pressure, heart rate, respiratory rate, O2 saturation and the need for intervention to maintain respiratory status, times were measured as secondary outcomes.

Statistical Analysis

Samples were selected using convenient (simple) sampling method. The sample size was calculated as 60 for each group using the formula

$$n = \frac{(z_1+z_2)^2(s_1^2+s_2^2)}{d^2}$$

Where Z1 is 95% confidence interval or 1.96, Z2 is 80% test power or 0.85, S1 is the estimation of standard deviation from each of the variables of both groups which was considered as 0.83 and d is the least difference between the mean of each variables of both groups which showed a significant difference and was considered as 0.5.

All of the achieved data were logged into the SPSS software (version 24). Chi-square, independent t-test and Mann Whitney tests were used for evaluating the differences between both groups and ANOVA test with repeated measures was used for comparing the changes in the results of each group. Also the number (percent)

and mean \pm standard deviation for both groups were presented and the level of significance was set at $p < 0.05$.

Results

In the present study, patients were divided into two groups of Propofol-Ketamine (22 boys and 13 girls with a mean age of 7.47 ± 3.22 years) and Propofol-Sufentanil (21 boys and 14 girls with a mean age of 6.24 ± 3.42). No significant difference existed between both groups regarding their age, gender, weight and UMSS sedation score ($P > 0.05$) but pain intensity (UPAT) was significantly lower in the Propofol-Ketamine group compared to the Propofol-Sufentanil group ($P: 0.03$) (Other information is presented in Table 2).

According to the gained information in the present study, no significant difference existed between both groups regarding their HR, SPO₂, SBP, DBP, and MAP before, during and after the procedure ($P > 0.05$) but, HR was significantly lower in the PK group before the intervention compared to the PS group ($P: 0.02$).

Also analysis of variance with repeated measures showed that changes in HR, SPO₂, SBP, DBP and MAP at different times (before, during and after the procedure) in each group have been statistically significant ($P < 0.0001$ for every measurement).

It must be noted that no significant difference existed between both groups regarding the type of performing procedure and post-surgical complications (nausea and vomiting) ($P > 0.05$). Also, 58.8% of the Propofol-Sufentanil group and 21.1% of the Propofol-Ketamine group had movement during the surgery; 55.9% of the Propofol-Sufentanil group and 24.2% of the Propofol-Ketamine group received repeated doses of the sedative drug. So the level of movements and the need for repeated doses of sedative were significantly lower in the Propofol-Ketamine group compared to the Propofol-Sufentanil group ($P < 0.05$). Furthermore, no significant difference was observed between both groups regarding different recorded times, including the onset of the drug's effect, time interval between the end of the procedure and the patient's awakening, and duration of recovery ($P > 0.05$). It must be noted that 2 patients from the Propofol-Ketamine group and one patient from the Propofol-Sufentanil group were excluded from the study due to the changes in their anesthesia plan.

Discussion

In the present study no significant difference existed between two groups of Propofol-Ketamine and Propofol-Sufentanil regarding their vital signs before, during, and after the procedure, complications and the time durations of the procedures; but the rate of movement during the procedure, the need for repeated doses, and the quality of sedation and intensity of pain was significantly lower in the Propofol-Ketamine group compared to the Propofol-

Sufentanil group.

Therefore, using the combination of Propofol-Ketamine for inducing sedation in children with acute lymphoblastic leukemia undergoing diagnostic procedures such as LP, BMA and BMB is better than Propofol-Sufentanil.

In the study of Anghelescu et al., the sedative effect of two doses of 1 mcg/kg and 0.5 mcg/kg of fentanyl along with Propofol and local anesthesia was compared in 162 children with ALL or lymphoblastic lymphoma undergoing painful procedures. Fentanyl with the dose of 1 mcg/kg decreased the dose of Propofol, rate of movements and recovery time (2).

Also, in the study of Ghasemi et al., general anesthesia with Fentanyl and Propofol was suggested as an appropriate for children with cancer undergoing painful procedures such as BMA, BMB and IT (23).

In the study of Hollman et al., the combination of Propofol-Fentanyl was compared to Propofol solely for performing LP in children with acute lymphoblastic leukemia; the authors concluded that the combination of Propofol-Fentanyl had more effect, less need for repeated doses and less side effects compared to Propofol (24).

In the study of Hooke et al., Propofol was suggested as a supplementary medicine for pain management in children with cancer (25).

A study that compared the effect of the combination of Propofol-Ketamine with Propofol alone on induction of sedation in an emergency center concluded that the combination of Propofol-Ketamine could not decrease respiratory depression in comparison to Propofol alone and also, administration of ketamine along with Propofol would decrease the need for Propofol and increase patient satisfaction and level of sedation (26). In another study that compared two combinations of Propofol-Ketamine and Propofol-Fentanyl in a specialized anesthesiology center, it was concluded that the combination of Propofol-Fentanyl would significantly decrease the pulse and systolic and diastolic blood pressure compared to the combination of Propofol-Ketamine. In this study also administration of the combination of Propofol-Ketamine led to a more appropriate hemodynamics in comparison to the combination of Propofol-Fentanyl; it was stated in the conclusions that administering both of these drug combinations is appropriate because they both would lead to rapid and safe induction of anesthesia with few side effects and mild hemodynamic effects (18). The study of Andolfatto et al., suggested the combination of Propofol-Ketamine as an effective method of sedation in children, because this combination was associated with less complications, shorter recovery period and higher satisfaction rate (13). Despite the researches on the effect of different medication on reduction of pain intensity and the amount of need for analgesics during and after surgery, there is still no general consensus (28-30).

According to the results of this study it seems that

Table 2. Hemodynamic changes, complications during and after the procedure, the rate of movement during the procedure, and the need for repeated doses in both of the groups.

| Variable | | Propofol-Ketamine group | Propofol-Sufentanil group | P value |
|--|---|-------------------------|---------------------------|---------|
| Heart rate (mean ± SD) (per minute) | Before the procedure | 102.17 ± 16.47 | 109.74 ± 24.36 | 0.02 |
| | During the procedure | 106.1 ± 15.05 | 103.38 ± 19.92 | 0.18 |
| | After the procedure | 98.90 ± 13.44 | 99.14 ± 21.68 | 0.08 |
| Arterial oxygen saturation (mean ± SD) (percent) | Before the procedure | 98.20 ± 0.90 | 98.05 ± 1.30 | 0.28 |
| | During the procedure | 99.72 ± 1.76 | 99.47 ± 1.76 | 0.10 |
| | After the procedure | 99.18 ± 1.07 | 99.35 ± 0.91 | 0.30 |
| Systolic blood pressure (mean ± SD) (mmHg) | Before the procedure | 113.74 ± 13.91 | 109.54 ± 11.32 | 0.33 |
| | During the procedure | 114.75 ± 12.16 | 97.02 ± 14.43 | 0.16 |
| | After the procedure | 113.09 ± 14.34 | 95.4 ± 13.59 | 0.79 |
| Diastolic blood pressure (mean ± SD) (mmHg) | Before the procedure | 75.57 ± 12.78 | 71.54 ± 15.61 | 0.29 |
| | During the procedure | 76.51 ± 14.12 | 59.11 ± 17.36 | 0.35 |
| | After the procedure | 74.03 ± 13.01 | 56.17 ± 11.45 | 0.43 |
| Average arterial pressure (mean ± SD) (mmHg) | Before the procedure | 94.17 ± 13.38 | 86.88 ± 15.17 | 0.47 |
| | During the procedure | 94.28 ± 11.81 | 73.73 ± 15.17 | 0.14 |
| | After the procedure | 88.75 ± 11.71 | 72.82 ± 12.31 | 0.69 |
| Complication | Nausea and vomiting | 0 | 1 (3%) | 0.30 |
| Procedure | IT | 10 (28.6%) | 13 (37.1%) | 0.57 |
| | BMA | 14 (40%) | 11 (31.4%) | |
| | BMA/IT | 10 (28.6%) | 8 (22.9%) | |
| | BMA/BMB | 1 (2.9%) | 3 (8.6%) | |
| Movement during the procedure | | 7 (21.2%) | 20 (58.8%) | 0.002 |
| The need for repeated doses of the drug | | 8 (24.2%) | 19 (55.9%) | 0.008 |
| Time duration (Minutes) | Effect onset | 2.78 ± 0.99 | 2.55 ± 2.78 | 0.37 |
| | Duration of the procedure | 11.84 ± 3.08 | 12.26 ± 2.73 | 0.47 |
| | Interval between the end of the procedure and patient's awakening | 7.87 ± 1.21 | 7.39 ± 2.22 | 0.63 |
| | Recovery | 29.18 ± 8.24 | 29.73 ± 10.28 | 0.87 |

BMA: bone marrow aspiration, BMB: bone marrow biopsy, IT: intrathecal

Propofol in combination with other sedative drugs, such as Sufentanil and Ketamine is safe and effective for the management of painful procedures like Lumbar Puncture, and it seems that the combination of Propofol-Ketamine could be better than Propofol-Sufentanil in providing high quality sedation, relieving the pain, decreasing the movements and the need for repeating the drug dosage.

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