

Ketofol for Procedural Sedation and Analgesia in Children with Acute Lymphoblastic Leukemia

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Abstract

Objectives: The aim of this work is to study the effects, adverse effects and recovery time of IV mixed propofol and ketamine (ketofol) in 3:1 ratio as a sedative analgesic in children with acute lymphoblastic leukemia undergoing bone marrow aspiration

Methods: This was a prospective, observational pilot study of twenty patients; 3-12 years with ALL requiring sedation for BMA were included. Mixture of ketofol (3:1) was administered intravenously in a dose of 0.5 mg/kg at 30-second to 1-minute intervals aiming to achieve a sedation level of 3 or 4 on Ramsay scale to start the procedure. Patient satisfaction was the primary outcome in our study. Faces pain scale-revised (FPS-R) was used to assess the degree of analgesia. Secondary outcomes included sedation time, recovery time, adverse events and safety.

Results: 20 patients were enrolled for the study. The median dose of ketofol is 3 mg/kg of propofol and 1 mg/kg of ketamine with no patients required extra doses. The median score on the pain faces scale was (comfortable) (1-3; 95% CI 1.08-2.92). Median recovery time was 22 minutes (16-30; 95% CI 14.08-29.32). The cardiorespiratory adverse events were transient, tolerable and easily corrected.

Conclusion: Combination of ketamine and propofol in the same syringe in this pilot study produced effective sedation, which is illustrated by the degree of satisfaction shown by patients. Moreover, rapid recovery and absence of clinically significant adverse events were noticed among children requiring procedural sedation and analgesia for bone marrow aspiration. A high recommendation of using large sample size should be considered for further assessment and verification of our results.

Keywords: Propofol; Ketamine; Sedation; Analgesia; Acute lymphoblastic leukemia; Bone marrow aspiration

Introduction

Children with acute lymphoblastic leukemia need regularly invasive procedures, such as lumbar puncture and bone marrow aspiration, for follow up [1]. Those children require sedation to accomplish the procedures. To achieve sedation with adequate analgesia, we need an agent not only has rapid onset and a smooth recovery period, but should also provide adequate cardiovascular and respiratory function, amnesia, and motor control throughout the procedure [1]. As there is no single agent that currently available offering these qualities, physicians are enforced to use mixture of different drugs at varying doses to achieve their target [2].

Propofol is a non-opioid, non-barbiturate, sedative-hypnotic agent with rapid onset and short duration of action. It has anti-emetic effects and reliably produces sedation [3]. Dose-dependent cardiovascular depression [4], respiratory depression and bradycardia are the most hazardous side effects [3]. Propofol has no analgesic effects, which is a challenging event during painful procedures [3].

Ketamine is a NMDA receptor antagonist, neuroleptic anesthetic [5,6] that produces satisfactory analgesia, sympathetic nervous system stimulation, and increased blood pressure and heart rate. Ketamine, unlike propofol, produces cardiovascular and respiratory depression to lesser extent, and protects the airway by minimally affecting airway reflexes and spontaneous respiration [1]. However, Ketamine is like

any other drug, carries a major drawback which is the incidence of dose-related emergence reactions, which may include nightmares or vivid hallucinations [1].

In spite of the minimal emergence phenomena, hemodynamic and respiratory stability was illustrated in previous studies through the sympathomimetic effects of ketamine, which can oppose the cardiovascular depressant effects of propofol [7].

The combination of ketamine and propofol mixed in one syringe (so-called "ketofol") has been shown to be effective in the operating room, ambulatory settings and emergency departments [3,8-12]. There is a very little knowledge about ketofol in the scientific literature about its use in bolus form for procedural sedation and analgesia (PSA). A ketamine-propofol syringe admixture in a newly published non-comparative, prospective evaluation of ketofol in the emergency setting was found to be safe, with rapid recovery time and high patient satisfaction scores [3].

However, there is a little number of studies in pediatric patients describing protocols employing ketofol in bolus form for PSA in a non-operating-room setting [13,14]. Therefore, we designed this pilot study to assess the effects, adverse effects and recovery time of IV mixed propofol and ketamine (ketofol) in 3:1 ratio as a sedative analgesic in children with acute lymphoblastic leukemia undergoing bone marrow aspiration.

Methods

The institution's Research Ethics Committee approved this prospective, observational pilot study. Informed written consent was obtained from the parents or legal guardians of the patients, and agreement was obtained from children older than 7 years after clarifying the principle of the study. During a one year period, Children aged 3-12 years were enrolled in the study. Inclusion criteria were all consecutive children with acute lymphoblastic leukemia undergoing bone marrow aspiration admitted to the sedation room of the South Egypt Cancer Institute hospital. Exclusion criteria included previous sensitization or anaphylactic reaction to propofol, ketamine, soy or egg products; low blood pressure or hemodynamic instability; evidence of head injury, raised intracranial or intraocular tension; use of drugs known to interact with either study agent; and an American Society of Anesthesiologists (ASA) physical status score greater than 2.

In accordance with guidelines published by the American Academy of Pediatrics and the ASA, ketofol was given [15,16]. All members of the care team at the procedural sedation room had Pediatric Advanced Life Support certification.

Both before and during sedation, continuous monitoring of oxygen saturation was carried out, and non-invasive blood pressure was recorded every five minutes. Peripheral intravenous access was obtained, and sedation with ketofol was started after baseline vital signs were recorded. The principle investigator was present throughout the procedure. He was prepared to emergency situations for airway patency establishment and maintenance, ventilation control with a bag valve-mask and tracheal intubation when needed, during the procedure.

Airway management equipment was available beside all patients. All patients did not receive oxygen supplementation unless it was required; they were on room air throughout the procedure. The study investigator was monitoring and recording patient recovery after the procedure. Discharge criteria were as follows: (i) sufficient oxygenation with airway patency, (ii) awake or easily aroused (minimal tactile or vocal stimulation might be necessary), (iii) presence of swallowing reflex, with the ability to swallow clear liquids while protecting the airway, and (iv) achieving pre-sedation level of responsiveness.

Intervention

Ketofol was prepared as a 3: 1 mixture of propofol 30 mg/3 ml and ketamine 10 mg/3 ml mixed in a 10 mL syringe. The mixture was administered over 10–20 s through a peripheral venous cannula. No premedication was given. Ketofol was given intravenously in a dose of 1 ml at 30-second to 1-minute intervals aiming to achieve a sedation level of 3 or 4 on Ramsay scale to start the procedure [17]. During the procedure, extra doses of ketofol were administered at 2-min intervals if needed. A normal saline flush followed each ketofol dose before subsequent doses were injected.

Outcome measures

All data were registered in a standard data collection record, which included age, weight, medications, doses administered, total sedation time (time passed from initial sedative injection to spontaneous eye opening), recovery time (time passed from the end of the procedure to awakening), vital signs, adverse effects and interventions. The administered dose of ketofol is expressed as the amount of each of the

ketamine and propofol constituent, reported in milligrams per kilogram of bodyweight. To consider procedural sedation and analgesia with ketofol efficacious, the required procedure must be completed without adjunctive medications. Ramsay score shown in Table 1, was used at the end of each procedure.

1	Nervous, agitated, and/or restless.
2	Cooperative, orientated, quite patient.
3	Only obeying orders.
4	Sleeping, hitting the glabella, and responding to high voice suddenly
5	Sleeping, hitting the glabella, and responding to high voice slowly
6	No response to any of these stimulations

Table 1: Ramsay sedation score

Post-procedure, pain faces scale was used to assess the patient's satisfaction. Physicians performing the procedure were asked if they were satisfied, very satisfied, unsatisfied or very unsatisfied with the sedation. Vital sign changes compared with preprocedural levels were reported, as the difference was recorded immediately after the procedure. Complications (oxyhemoglobin saturation less than 90%, apnea, hypotension, administration of i.v. fluids for volume expansion, vomiting, or emergence reaction) were recorded during the procedure.

We stated that minor airway adverse events are the need for manual manipulation of the airway [18]. While major adverse events of the airways were figured as the need for bag-valve-ventilation, tracheal intubation or pharmacological reversal of respiratory depression [18]. Desaturation was defined as sustained hypoxemia (an oxygen saturation <90% or 10% below the baseline for more than 30 s). Hypotension was defined as a decrease in systolic blood pressure >20% from baseline [18].

Patient satisfaction was the primary outcome in our study. Secondary outcomes included sedation time, recovery time, adverse events and safety.

Statistical analysis

Descriptive measures are presented according to the variable characteristics. Data are expressed as numerical values and percentages or mean and standard deviation (SD) for categorical variables, and as medians for continuous variables. Where appropriate the 95% confidence interval (CI) was calculated. Using the paired t-test, the differences in means were tested. Probability values less than 0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS (software statistical computer package version 16).

Results

A total of 20 patients were enrolled for the study. Median patient age was 8.5 years and 70% of them were males.

Table 2 shows the characteristics of the patients undergoing PSA for bone marrow aspiration.

The median dose of ketofol administered was 3 mg/kg of propofol and 1 mg/kg of ketamine (range: 2.4–5.1 mg/kg; 95% CI 1.78–4.22 mg/

kg). All 20 procedures were completed successfully, with no adjunctive medications required. No extra doses were needed.

	Median	95% CI
Age (years)	8.5	1.27-13.63
Weight (Kg.)	26	10.86-33.74
Total sedation time (min.)	26.5	15.11-39.39
Recovery time (min.)	22	14.08-29.32
Gender (M/F)	14/6	70%/30%

Table 2: Patients' characteristics

The median score on the pain faces scale was 2 (range: 1–3; 95% CI 1.08–2.92). Satisfaction of physicians with sedation was reported in 19 out of 20 (95%) procedures. Median recovery time was 22 minutes (16–30; 95% CI 14.08–29.32). Vital sign changes are summarized in Table 3.

	Mean change	95% CI	P. value
HR	-8.3	(-27-11.1)	0.001
BP	-6.3	(-28.14-15.54)	0.01
RR	-1.1	(-4.48-2.28)	0.017
SpO2	-0.45	(-3.17-2.27)	0.164

Table 3: Vital sign changes

In spite of experiencing decreases in heart rate, blood pressure and respiratory rate, no patients showed evidence of neither poor perfusion nor significant statistical desaturation during the procedure. No assisted ventilation or airway repositioning was needed. Regarding hypotension, 5 cases (25%) experienced transient decrease in blood pressure, for which IV saline was required to maintain hemodynamic stability. The median value of the IV saline injected was 60 ml, ranging from 50–120 ml. 4 (20%) cases reported a temporary decrease in SpO₂ that needed a simple O₂ mask to alleviate hypoxia. No salivation, vomiting nor agitations were reported. Recovery periods were non eventual with little or no residual drowsiness, unsteadiness, or nausea. Side effects are summarized in Table 4.

Discussion

Bone marrow aspiration has a significant role in the management of children with acute lymphoblastic leukemia. As this procedure causes moderate to severe pain and anxiety, sufficient analgesia and sedation should be guaranteed while it is carried out. The preliminary results of this study show that PSA with ketofol during bone marrow aspiration in children provides patient analgesia as well as transient tolerable respiratory and hemodynamic adverse events. A short recovery time (median: 22 minutes) was observed in our study.

Variable	N (%)
Hypotension	5 (25%)
Hypoxia	4 (20%)
Apnea	0 (0%)

Vomiting	0 (0%)
Agitation	0 (0%)
Salivation	0 (0%)

Table 4: Side effects

There are many pediatric studies which have announced the separated use of ketamine and propofol for cardiac catheterization [19–21], auditory brainstem response testing [22], magnetic resonance imaging [23], gastrointestinal endoscopy [24], burn dressing changes [20], fracture reduction [13] and oncology procedures [25,26]. However, the mixture and dosage of ketofol administered without administration of extra drugs has been examined in few studies in different ratios [4,8].

When mixed together in the same syringe, ketamine and propofol have been shown pharmaceutical compatibility [27]. The aim of combination of anesthetics is to obtain high therapeutic activity with low adverse effects. The addition of ketamine to propofol decreases the levels of both hypnotic and anesthetic doses of propofol, resulting in tolerable adverse event and recovery time profiles [3]. While the nauseant and psychic recovery effects of ketamine are antagonized by the sedative and antiemetic effects of propofol [3]. The interest in ketofol arouse from that, mixing ketamine with propofol as a PSA regimen, allows using lower drug doses than those typically required for each agent alone. Moreover, combining ketamine with propofol allow maintaining hemodynamics and preserving airway patency and respiratory function to some extent [2,26].

The theoretically compelling drug combination accounts for the balance between the sedative and antiemetic effects of propofol with the nauseant and psychomimetic effects of ketamine. The ability to achieve deep sedation with lower doses of ketamine may allow for shorter recovery times compared to using of ketamine alone.

Furthermore, during propofol PSA, ketamine provides an analgesic effect resulting in fewer adverse airway effects that may eliminate the need for using fentanyl as analgesic with propofol [28]. Fentanyl/midazolam, morphine/midazolam, and ketamine/ midazolam are three common combinations used in “balanced” PSA. When using an opioid and benzodiazepine, the opioid should be titrated to take effect first, followed by the benzodiazepine for further sedation [29]. 20–30% of patients experienced respiratory depression when receiving a combination of opioid and benzodiazepine [18,29]. In a study by Kennedy et al., [29] mixing ketamine with midazolam was reported to be more effective as analgesic and anxiolytic with little respiratory depression compared to fentanyl and midazolam. However, the ketamine and midazolam combination group had a higher incidence of emesis and longer sedation recovery times. Studies using ketofol in children have shown lower rates of respiratory depression (0.9–15%), [3,13,14] absence of vomiting episodes and a short recovery time, which raises the desire of using this drug for procedural sedation and analgesia in children.

Using propofol alone as a sedative in children resulted in total doses of propofol between 2.8 and 3.5 mg/kg [14]. An important finding of our study was that the median dose of ketofol administered was 3 mg/kg. However, the median dose of our study was higher than the median dose of 0.75 mg/kg previously illustrated [3]. This difference may be resulted from differences in patient populations. The inclusion criteria in the cited study enrolled adult patients. The higher doses of

ketofol used in our study may be explained by the requirement of deep sedation in pediatric patients undergoing invasive procedures to prevent excessive motion and to reduce pain and anxiety. The median sedation score at the end of the procedure was 5, illustrating our point of view. The median recovery time in our study was 22 min. This result is in relatively similar to the median recovery time reported by studies in children using the propofol/ketamine combination (6.5 min–23 min). [13,22,23,30,31] While using ketamine only, pediatric studies have reported median recovery times ranging from 32 min to 103 min [32-36]. Also, studies that evaluated the use of propofol only have shown recovery times ranging from 8 min to 93 min [37-41] and time for procedure onset between 1 min and 8 min.

As a desired end-point of a procedural sedation and analgesia regimen, short recovery time is an important target. There is evidence supporting the requirement of a well trained health-care professional to observe each sedated patient until recovery is well established [42]. The shorter the time committed to patient sedation, will release both physician and nurse to care for other patients [43]. The level of patient and physician satisfaction in our study was comparable to the 90% level of satisfaction illustrated in previous studies evaluating use of ketamine only [32,33,35].

Our patients experienced clinically non-significant transient decrease in pulse rate and blood pressure. Similar results regarding hemodynamics were shown by Amorniyotin S et al, 2012 [44]. There were only 5 cases of hypotension, which was temporary, tolerable and easily corrected by IV saline administration. These findings may differ from those shown by other pediatric studies assessing the combination of propofol-ketamine [45]. This difference may be attributed to the usage of one single dose of ketofol at the beginning of the procedure, in our study, rather than dividing it at intervals as reported by Coulter FLS et al, 2014. [45]. Even though respiratory depression was mild and did not need airway intervention, its occurrence raises the importance of close observation and monitoring.

The most seen adverse effects related to ketamine are emergence reactions or hallucinations, which will occur more commonly when ketamine is used alone. It has been reported that the mixing ketamine with propofol decreases this undesirable effect [46]. Our study confirms these data, as no patient reported dreams during sedation with ketofol. In addition, diplopia and nystagmus are much less frequent after propofol anaesthesia [42]. In our study, vomiting was not observed. The incidence of excessive salivation has often been shown as one of the adverse-events of ketamine, which ranges from 1.7% to 12% [47,48]. The too small sample size, in our study, prevents us from observing such low incidence side effect.

This was a pilot study with a limited small number of patients. Thus, the hemodynamic and respiratory changes observed during this study represent a preliminary data and should be taken with caution. Moreover, the safety and incidence of rare adverse effects were hindered because of the small sample size. The simple strategy of using a fixed combination of two drugs with a synergistic effect is very interesting and is worth further evaluation. These drugs should be given only in situations where the equipment and expertise for first aid are promptly present because of carrying out that procedural sedation and analgesia may call for advanced airway management.

Conclusion

Combination of ketamine and propofol in the same syringe in this pilot study produced effective sedation, which is illustrated by the

degree of satisfaction shown by patients. Moreover, rapid recovery and absence of clinically significant adverse events were noticed among children requiring procedural sedation and analgesia for bone marrow aspiration. A high recommendation of using large sample size should be considered for further assessment and verification of our results.

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