The use of ketofol for procedural sedation in paediatric bone marrow aspiration and intrathecal chemotherapy in children

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Abstract

Background: Procedural sedation is an effective component of care in paediatric oncology for painful diagnostic and therapeutic procedures. The aim of this study was to evaluate the safety and efficacy of ketamine/propofol combination in procedural sedation for the bone marrow biopsy and intrathecal chemotherapy in paediatricpatients in the paediatric oncology ward.

Methods: Fourteen paediatric oncology patients at the Paediatric oncology ward of the Lagos University Teaching Hospital, Idi- Araba, Lagos who were to have bone marrow biopsy and intrathecal chemotherapy and were in need for proceduralsedation were included in this study. An initial bolus dose (500 mcg/kg) of ketamine/propofol1:1 (ketamine 8 mg/ml and propofol 8 mg/ml) was given to all patients followed by top up at a dose of 10 mcg/kg to achieve Ramsay Sedation Scale of 4.

Results: The mean age of the patients was 6±2 years. The median initial bolus dose of ketofol administered was 5 ml of aliquot with median dosage of 6 ml (range: 4.8–7.5 ml) only three patients (21.4%) needed the dose to be increased to achieve Ramsay score 4. Only one patient experienced hypotension due to hypovolemia secondary to persistent vomiting prior to procedure

Conclusion: Intravenous administration of ketofol may provide adequate and safe procedural
sedation for oncology patients in the paediatric oncology ward, with rapid recovery and no clinically significant complications. Further studies with larger number of patients are required to evaluate and validate these findings.

Keywords: Ketamine, propofol, procedural sedation, bone marrow, biopsy.

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Introduction

The number of noninvasive and minimally invasive procedures performed outside of the operating room has grown exponentially over the last several decades. Sedation, analgesia, or both may be needed for many of these interventional or diagnostic procedures.[1] The aim of using sedation is to reduce stress; and to provide anxiolysis, analgesia and amnesia without compromising the cardiovascular and respiratory system[1].

The drugs commonly used for sedation include alpha 2 agonists, benzodiazepines, etomidate, antipsychotics and propofol, none of which meets the criteria of an ideal sedative. Multiple studies have evaluated the safety of intravenous ketamine/propofol combination ("ketofol") in the same syringe in the children emergency department and operating room.[2,3]

Ketamine; a dissociative anaesthetic agent is classified as a N-methyl D aspartate [NMDA] receptor antagonist and has also been found to bind to opioid receptors and sigma receptors. It induces a state referred to as "dissociative anesthesia."[4] It provides amnesia, analgesia and anesthesia while maintaining protective airway reflexes and spontaneous respiration.[1,5] Its significant adverse effects include its propensityto cause vivid and frightening emergent reactions,[6] sympathomimetic effects and vomiting when administered in sedating doses[7]

Propofol; 2,6 di-isopropyl phenol, is a short-acting intravenously administered sedative and hypnotic agent.[8] It is indicated in the induction and maintenance of general anesthesia, sedation for intubated, mechanically ventilated patients in the ICU, and in procedures such as colonoscopy. It lacks analgesic properties and painful on injection.[8]The adverse effects related to the use of propofol include dose-dependent hypotension and respiratory depression[9-11]

Ketamine and propofol are physically compatible with no increase in particle content at Y site injection[12]. Ketofol (ketamine/propofol combination) have been

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used for procedural sedation and analgesia (PSA) widely in the operating room and emergency department[2,3,] but not in the ward setting as monitored care. Most of the potential side effects of sedatives are dose-dependent, and when administrating this combination the doses of each drug can be reduced leading to increased safety and efficacy with minimal adverse effect.[13]

The use ketofol is considered a relatively new idea for most practitioners, there is very little or nearly no data available in scientific literature for its use as a sedative in the paediatric oncology wards in our environment. The aim of this study was to evaluate safety and efficacy of ketofol for procedural sedation for oncology patients in the pediatric oncology unit requiring interventional subarachnoid chemotherapy and bone marrow aspiration.

Materials and Methods

After approval of this case series prospective study by the local Ethics Committee of Lagos University Teaching Hospital and consent of parents/guardian, paediatric oncology patients requiring bone marrow biopsy and needing subarachnoid/intrathecal chemotherapy and in need for sedation were included. Exclusion criteria include patients above 18 years old, as well as patients with known allergies to the studied drugs.

Ketofol (propofol/ketamine admixture) was prepared by an assistant who was not involved in the clinical management of the studied patients. Ketofol (1:1): propofol 8 mg/ml, ketamine 8 mg/ml by mixing 10 ml propofol 1% (10 mg/ml) with 2 ml ketamine (50 mg/ml) and 0.5 ml of injection water (each ml of aliquot contained 8 mg propofol and 8 mg ketamine) to make a total of 12.5mls. Intravenous ketofol as an initial bolus of 500 mcg/kg IV of aliquot, followed by top up of 10 mcg/kg to achieve Ramsay Sedation Scale[14] of 4.The Ramsay score (target and actual) was recorded during the procedure. Patients were continuously monitored according to study protocol. Respiratory rate, blood pressure, oxygen saturation were recorded before and during the entire procedure, development of side effects, recovery time and Aldrete score were recorded. Systolic blood pressure (SBP) and heart rate (HR) were recorded before starting sedation (T0), then every 5 min throughout the procedural sedation. Afterward still patient was fully recovered and back to pre –procedure state targeting aldrete score of 9-10.[15]Complications including hypotension which is defined as an abnormally low blood pressure (BP) below the 5th percentile or below two standard deviations (SDs) of the mean for age and gender (SBP less than 60 mm Hg or > 15% drop from baseline) (Table 1); hypertension which is defined as an abnormally high blood pressure (BP) above the 5th percentile or above two standard deviations (SDs) of the mean for age and gender (SBP more than 120 or > 15% rise from the baseline), and respiratory depression (apnea more than 20s) were recorded. Recovery time was defined as the time required for the patient to regain the baseline conscious level (conscious level before starting sedation) after discontinuing sedation.

Statistical analysis

Continuous data were presented as mean±standard deviationor median, categorical data were presented as number and percent. ANOVA was used to compare the recorded hemodynamic parameters where P values less than 0.05 was considered significant. SPSS 20.0 (Statistical Package for the Social Sciences) was used for statistical calculations.

Results

A total of 14 children were enrolled for the study. Median patient age was 6 ± 2years and 57.1% were females. All patients were well sedated. Patients had 15 bone marrow biopsies and 35 intrathecal injections.

Table 1.Haemodynamic changes in children with ketofol use

	T0	T1 [5min]	T2 [10min]	T3 [15min]	T4 [20min]	T5 [25min]	T6 [30min]
SBP	102.4±16.2	99.2±13.7	99.8±14.4	108.9±14.1	99.6±11.9	98.2±14.7	104±14.5
HR	106.7±19.3	103±20.9	104±18.8	98.5±19.8	90.1±18.8	93.5±18.3	96.2±18.5

The median initial bolus dose of ketofol administered was5 ml of aliquot with median top up dose of 6 ml (range: 5–7.5 ml). There were no significant changes observed in pulse rate and blood pressure except one patient (7.1%) who became hypotensive due to repeated vomiting successfully resuscitated with intravenous crystalloid fluid therapy. The median recovery time was 30 min (range 20–64 min).No significant complications such as desaturation, respiratory depression and agitation were detected.

Discussion

The main finding of the current study was that, intravenous administration of a combination of ketamine–propofol (ketofol) in the same syringe was effective in maintaining Ramsay Sedation Scale 4 without hemodynamic instability for procedural sedation outside the operating room in children requiring bone marrow aspiration and subarachnoid chemotherapy in the ward. Significant haemodynamic changes in the form of hypertension, hypotension which are the hallmark of the studied drug when used singly as monotherapy at the recommended dose were absent except one patient who experienced hypotension due to

repeated vomiting prior to procedure and corrected with crystalloid administration with good results haemodynamics was consequently normalized without need for administration of vasopressor.

In line with our results, studies[16-18]have demonstrated the safety of using ketofol on hemodynamics. Willman *et al*[16] reported that no patient became hypotensive or had evidence of poor perfusion when ketofol was administered in a mean dose of (0.75 mg/kg of ketamine and 0.75 mg/kg of propofol) for PSA for mainly orthopaedic procedures conducted in the emergency setting. Andolfatto *et al*[17] demonstrated that only one patient out of 728 patients became hypotensive when ketofol was used for PSA for primarily adult orthopedic procedures. Furthermore, the effect of ketofol in procedural sedation was reported to have resulted in fewer significant hemodynamic compromise by investigators in another study[18]. The need for active interventions, including fluid or vasopressor administration as a result of significant haemodynamic disruption was small. This was attributed to the contradictory effect of both ketamine and propofol on autonomic nervous system, ketamine being sympathomimetic while propofol lessens this effect.

No respiratory depression or agitation was reported in the cohort group. Similar to our findings Willman *et al*[16]reported that three out of 114 had transient hypoxia who required bag-valve-mask ventilation, four patients required repositioning for airway mal-alignment, and three patients (2.6%; 95% CI 0.6–7.5%) had mild unpleasant emergence, of whom one received midazolam. Another study where investigators evaluated 728 adult orthopaedic patients for the effectiveness, recovery time, and adverse event profile of intravenous (IV) mixed 1:1 ketamine–propofol for procedural sedation and analgesia in the emergency setting. They reported that bag-mask ventilation occurred in 15 patients (2.1%), whereas recovery agitation occurred in 26 patients (3.6%) of whom13 (1.8%) required treatment[17].

The median recovery time in this study was 30 min (range 20–64 min) is higher than the findings of previous studies[17,19.] In an earlier report, Andolfatto et al[17]reported a median recovery time was 14 min (range 3–50 min). Erden *et al*[19]also reported mean recovery times were 12.1 and 13.6 min in the patient groups who underwent interventional radiological procedures under sedation with propofol 0.5 mg/ kg plus ketamine 0.5 mg/ kg and 0.25mg/kg respectively. The longer median recovery time in our study may be due to age related differences between the two studied populations as well as the lower dose of ketamine that was employed in those studies.

We had certain limitations. The study group was small and so reporting of adverse events was restricted. Also the study was not arandomized, blinded study and this may have introduced some bias.

In conclusion intravenous administration of ketofol provides adequate and safe sedation for paediatric oncology patients, rapid recovery with no clinically significant complications. As a result of the small size of this case series further studies with larger number of patients are required to evaluate and validate these findings.

Conflict of Interest

None declared in this work.

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