

Original Article

Ketofol for bone marrow aspiration and lumbar puncture in Children with ALL

Hashemi A MD¹, Ayatollahi V MD², Ghilian R MD³, Ghadami Yazdi A MD², Fadavi N MD⁴, Yadegari Y MD⁴, Shahri T BSc⁵, Mir Akhor M BSc⁵, Askari Nodoshan A BSc⁵, Pour Mohammadi Shahrabaki T⁵

- 1- Department of Pediatrics, Hematology, Oncology and Genetics Research Center, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 2- Department of surgery, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 3- Department of Internal Medicine. Hematology oncology and Genetics Research Center Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 4- Department of Pediatrics, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.
- 5- Bachelor of Nursing, Pediatric Ward, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.

Received: 30 June 2011
Accepted: 2 November 2011

Abstract

Background

Ketofol is usually using as a sedative drug during painful procedures now. That Provides sedation, analgesia and rapid recovery. The aim of this study was to compare the efficacy, respiratory and hemodynamic profiles, and side effects of two various combination of ketamine and propofol in patients undergoing bone marrow aspiration (BMA) and lumbar puncture (LP).

Materials and Methods

This randomized, double blinded study was designed to compare the quality of analgesia and side effects of intravenous ketofol in sixty boys and girls. In this study Patients received a slow bolus injection of a solution containing combination of equal amount of propofol and ketamine (1:1) (Group I) or two parts of propofol plus one part of ketamine (2:1) (Group II). Subsequent slow bolus injects to a predetermined sedation level using Ramsay Sedation Scale. Vital signs, oxygen saturation (SpO₂) and incidence of any side effects were recorded.

Results

Ketofol was used in 49 surgical procedures in children with a median age of 5 years (1 to 10 years old). In this study there was an increase postoperative nausea, psychomimetic side effects, and increase recovery time with the largest ketamine dosage (Group I). (P-value<0.001)

Conclusion

The adjunctive use of smaller dose of ketamine in ketofol combination minimizes the psychomimetic side effects and shortens the recovery time. A large number of patients are required to evaluate and validate these findings.

Key words

Propofol, Ketamine, Child, Analgesia

Corresponding Author

Ghilian, Rozita. MD. Internal Medicine. Hematology oncology and Genetics Research Center Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

Introduction

The great majority of patients with childhood leukemia become long-term survivors (1). Major advances have been achieved in the treatment of children with acute lymphoblastic leukemia (ALL) (2). Specific subgroups of patients characterized by age and initial white blood cell count at the time of diagnosis have been identified who have a 5-year disease-free survival rate greater than 80% (3). With the rising number of long-term survivors, increased attention has been directed towards possible long-term effects of leukemia and its treatment. Presently, most therapeutic protocols for the treatment of childhood acute lymphoblastic leukemia incorporate some form of central nervous system prophylaxis. The majority of regimens include craniospinal radiation or cranial radiation plus intrathecal chemotherapy (4). Thus lumbar puncture or bone marrow aspiration in pediatric patients with ALL is often repeated at regular intervals. An ideal procedural sedation agent should not only have rapid onset and a smooth recovery period, but should also provide sufficient analgesia, sedation with adequate cardiovascular and respiratory function, amnesia, and motor control immobile throughout the procedure (5).

There has been increasing interest in the use of propofol, a nonopioid nonbarbiturate sedative hypnotic, for pediatric procedural sedation. Propofol's advantages include its rapid onset, short recovery time, and antiemetic effects (7). Propofol is a short-acting intravenous sedative agent used for the induction and maintenance of general anesthesia for adults and children (8). Adverse effects include dose-related cardiovascular and respiratory depression and bradycardia (9). Propofol also lacks any analgesic effect, and thus some clinicians may combine an analgesic medication with propofol sedation for painful procedures. While providing analgesia prior to procedural sedation is considered standard care, the provision of narcotic analgesia during procedural sedation is controversial. It has been shown that the addition of alfentanil, an ultra-short-acting opioid, during procedural sedation with propofol does not result in a difference in reported pain or recall immediately after the procedure, but is associated with an increase in the proportion of patients requiring stimulation to induce breathing (10).

Procedural sedation and analgesia (PSA) in children is commonly accomplished using intravenous (IV) or intramuscular (IM) ketamine, a dissociative sedative known to reliably produce analgesia and amnesia (11). Ketamine is classified as an 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". Ketamine is a phencyclidine anesthetic that produces intense analgesia, sympathetic nervous system stimulation, and increased blood pressure and heart rate. Unlike propofol, ketamine causes minimal cardiovascular and respiratory depression, and patients maintain protective airway reflexes as well as spontaneous respiration. A major drawback of ketamine is the incidence of emergence reactions at increasing doses, which may include nightmares or vivid hallucinations (5). There are numerous reports of ketamine efficacy and safety in pediatric PSA (7). Previous studies have shown that the cardiovascular depressant effects of propofol can be offset by the sympathomimetic effects of ketamine, resulting in stable hemodynamic and respiratory profiles and minimal emergence phenomena (12). Ketamine has been shown to provide analgesia in acutely painful conditions in the ED setting (13) and may represent an analgesic option with fewer adverse effects than fentanyl when combined with propofol sedation (14-16).

The combination of ketamine and propofol has received interest as a PSA regimen that allows the provision of PSA using drug doses lower than typically required for each agent alone, while the nausea and psychic recovery effects of ketamine are counterbalanced by the sedative and antiemetic effects of propofol (17-18). Ketofol (ketamine/propofol combination) was used for procedural sedation and analgesia. Ketamine and propofol are physically

compatible for 1 hr at 23°C with no increase in particle content at Y site injection (19). Ketamine–propofol combination appears to provide rapid, reliable, and effective ED PSA with short recovery times and few adverse events. However, there is a paucity of studies in pediatric patients describing protocols employing ketofol in bolus form for PSA in a non-operating-room setting (20-21).

Our goal was to compare the effectiveness, adverse effect profile, and recovery time of IV mixed ketamine and propofol (“ketofol”) in 1:1 ratio and 1:2 ratio for procedural sedation and analgesia in children with hematological diseases.

Materials and Methods

This was a randomized, double blinded study of procedural sedations using ketofol in pediatric patients with ALL requiring sedation in Shahid Sadoughi hospital in Yazd. Written informed consent was obtained from the parents or legal guardians of the patients. Sixty patients of both sexes between 1-10 years were studied. Inclusion criteria were all consecutive children with hematological diseases undergoing bone marrow aspiration and lumbar puncture (LP) admitted to the sedation room of hospital. Exclusion criteria included prior sensitization or allergic reaction to propofol, ketamine, soy or egg products; hypotension head injury, increased intracranial or intraocular pressure; use of drugs known to interact with either study agent.

Sedation was administered in accordance with guidelines published by the American Academy of Pediatrics. The care team at the procedural sedation suite included a specialized pediatric team: pediatric intensivist, pediatric hematologist, third-year pediatric resident and pediatric critical care nurse practitioner. All members had Pediatric Advanced Life Support certification.

All procedures were performed in the ED in an area equipped with continuous oxygen saturation and cardiac monitoring and a complete airway and resuscitation cart. In accordance with regional PSA guidelines, all sedations required the attendance of a certified EP (the treating physician), registered nurse (RN), and respiratory therapist.

One group (Group I) received ketofol that was prepared as a 1:1 mixture of 10 mg/ml propofol and 10 mg/ml ketamine and others in 2:1 ratio (Group II). PSA with ketofol was performed using titrated aliquots of medication (0.5 mg/kg of either component drug) at 30-second to 1-minute intervals at the discretion of the treating physician, with a target of deep or dissociative sedation (22). This was in accordance with our regional ED PSA guideline, and constitutes the usual practice in our ED. The principal investigator registered all data in a standard data collection record, which included age, weight, diagnosis, medications, doses administered, recovery time (time elapsed from the end of the procedure to awakening), vital signs, adverse events and interventions.

Statistical Analysis

Descriptive variables were analyzed using Students t-test and Mann-Whitney and K-square as appropriate using SPSS software statistical computer package version 15. Differences between the groups in mean blood pressure (BP), heart rate (HR), oxygen saturation and ketofol requirements were compared using analysis of variance with repeated measures. A P-value < 0.05 was considered to be statistically significant. Values are expressed as mean SD.

Results

A total of 49 procedures were enrolled for the study. 24 cases were in group I and 25 cases were in group II. Median patient age was 5 years and 46.9% were boys. There were no significant differences among patients in both groups regarding number of patients, age, sex, weight, ASA physical status. The mean dose of ketofol administered in group I was 1.8 mg/kg

of propofol and 1.8mg/kg of ketamine (range: 0.9–2.5 mg/kg; 95%CI 0.77–2 mg/kg) and in group II was 1.8 mg/kg of propofol and 0.9 mg/kg of ketamine. All 49 procedures were completed successfully, with no adjunctive medications required. Sedation scores were similar in both groups. Median score was 0 (range: 0–5; 25th–75th percentile 0–1.5; 95%CI 0.2–2.2) in both groups.

There was a minimal decrease in mean arterial blood pressure (MAP) from baseline in both groups following the initial dose of ketofol. All the patients had decrease in pulse rate compared to the baseline. The change was least in group II (89.91 \pm 7.21 vs. 116.63 \pm 8.48). ($p=0.06$), but no patient had severe tachycardia requiring treatment in both groups.

Patients in both groups did not have decrease in arterial oxygen saturation (SpO₂) and hypoxia after induction (SpO₂ <95%).

In group I, two patients (4.1%) complained of postoperative nausea, 12 patients (50%) experienced hallucinations. In group II no patient complained of postoperative nausea and 6 patients (24%) experienced hallucinations. (P -value=0.059)

Median recovery time in group I was 10.41 \pm 2.74 min and in group II was 4.64 \pm 1.58 min. (P -value<0.001)

Discussion

Bone marrow aspiration/biopsy and LP plays a central role in the management of ALL in children. As bone marrow aspiration causes moderate to severe pain and anxiety, adequate analgesia and sedation are required when the procedure is planned. The goals of procedural sedation are to provide an adequate level of sedation while minimizing pain and anxiety, maximizing amnesia, minimizing the potential for adverse drug-related events, controlling behavior, and maintaining a stable cardiovascular and respiratory status. Anesthetic drugs are often combined to increase therapeutic activity and decrease side-effects. The combination of ketamine with propofol reduces the levels of both hypnotic and anesthetic doses of propofol, resulting in favorable adverse event and recovery time profiles (9). The combination of ketamine and propofol has proved highly successful in anesthesiology for many years, but only recently has it begun to spread into other fields of medicine. Sedation with propofol alone in children requires total doses of propofol of between 2.8 and 3.5 mg/kg (21). Pediatric cardiology studies have shown that the use of ketamine reduces the dose of propofol required to achieve adequate sedation (23). Although the median dose of propofol in this series was low in comparison to studies using propofol alone for deep sedation, it was higher than the median dose of 0.75 mg/kg previously described (9). This difference may be the result of dissimilar patient populations.

We compared the safety and efficacy of different concentrations of ketofol in procedural operations in children. The combination of propofol and ketamine (2:1) provides effective sedation/analgesia during monitored anesthesia care. Badrinath et al, published One hundred female outpatients undergoing breast biopsy procedures under local anesthesia. They reported that combination of propofol and ketamine (5:1) provides effective sedation/analgesia during monitored anesthesia care (25).

Propofol in the recommended dose of 2-2.5 mg/kg almost always causes fall in blood pressure and the extent of fall depends upon the dose and adjuvant drugs used. The induction doses of propofol are reduced considerably by combination with small doses of ketamine. Ketamine had the additional advantage of better hemodynamic stability. Our patients experienced non-significant decreases in pulse rate and blood pressure. There were no cases of hypotension or bradycardia. This is similar to study of Silva et al that evaluate the effectiveness and safety of ketofol for procedural sedation and analgesia in children (26) and other pediatric studies evaluating the combination of propofol– ketamine (27-30).

In the other hand Daabiss et al compared the quality of analgesia and side effects of

intravenous different concentrations of ketofol in hundred children. The fall in MAP was mild (6%) and similar in both groups, combination of propofol: ketamine (1:1) and propofol: ketamine (4:1) (24). Akin et al published a trial of 60 patients undergoing cardiac catheterization who received sedation with propofol or propofol plus ketamine (3:1). They found a significant decrease in MAP in 11 patients in the propofol monotherapy group and three patients in the ketofol group (31).

The addition of low dose ketamine to propofol reduced the risk of respiratory depression and the need for repeat medication administration. Our results have confirmed the report of Akin et al in which there were no cases of desaturation in the ketofol group (31).

In contrast, Daabiss et al recorded the apnea and desaturation in both groups and end-tidal CO₂ increased slightly after induction (24). Willman and Andolfatto published a study of 114 patients requiring procedural sedation and analgesia mainly for orthopedic procedures were given a 1:1 mixture of propofol and ketamine. Transient hypoxia occurred in 2.6% of patients, out of them one patient required bag valve mask ventilation (32).

Short recovery time is an important and desirable end-point of a procedural sedation and analgesia regimen. There is compelling evidence supporting the need for a dedicated health-care professional to carefully observe each sedated patient until recovery is well established (33). By combining ketamine with propofol, clinicians have the ability to provide deep sedation using lower doses of ketamine, which may allow for more rapid recovery.

In this study the median recovery time of group II was shorter than group I. It is logical to expect that more rapid recovery may assist in ED patient flow, although total time in the ED was not specifically measured in this series, and no firm conclusions regarding the effects on patient flow can be made. While Akin et al in a trial of 40 adult patients undergoing endometrial biopsy reported that the combination of propofol (1 mg/kg) plus fentanyl (1 g/kg) was compared to the combination of propofol plus ketamine (2:1). Time to recovery was similar; however, time to discharge was longer in the ketofol group secondary to the increased presence of adverse events including nausea, vertigo, and visual disturbances (34).

It is thought that the sedative effects of propofol may mitigate adverse events such as recovery agitation and vomiting that are associated with ketamine use. In this series there were no post procedural vomiting recorded in group II.

Ketamine in sedative doses is associated with electroencephalographic activation. Furthermore, small-dose ketamine increases thalamic sensory output and arousal. The most frequent adverse reactions related to ketamine are emergence reactions or hallucinations. Sedative effects of propofol may be partially antagonized by the arousal effects of ketamine (35, 36). Our study confirms these data, the incidence of clinically significant hallucinations was noted in the large-dose ketamine group (group I).

In conclusion

The combination of ketamine and propofol (2:1) in a single syringe in this pilot study provided effective sedation, which is reflected by the high degree of satisfaction reported by patients. We observed rapid recovery and no clinically significant complications among children requiring procedural sedation and analgesia for bone marrow aspiration.

Acknowledgment

The authors would like to thank for Pediatric ward of Shahid Sadoughi hospital for their highly knowledgeable advices and support in the neuropsychological investigations.

References

1. Harila-Saari AH, Lähteenmäki PM, Pukkala E, Kyyrönen P, Lanning M, Sankila R. Scholastic achievements of childhood leukemia patients: a nationwide, register-based study. *J Clin Oncol*. 2007 Aug 10;25(23):3518-24.
2. Robison LL, Nesbit ME Jr, Sather HN, Meadows AT, Ortega JA, Hammond GD. Factors associated with IQ scores in long-term survivors of childhood acute lymphoblastic leukemia. *Am J Pediatr Hematol Oncol*. 1984 Summer;6(2):115-21.
3. Loh G, Dalen D. Low-dose ketamine in addition to propofol for procedural sedation and analgesia in the emergency department. *Ann Pharmacother*. 2007 Mar;41(3):485-92.
4. Arora S. Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: a review. *West J Emerg Med*. 2008 Jan;9(1):20-3.
5. Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). *Acad Emerg Med*. 2010 Feb;17(2):194-201.
6. Miner JR, Burton JH. Clinical practice advisory: Emergency department procedural sedation with propofol. *Ann Emerg Med*. 2007 Aug;50(2):182-7, 187.
7. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007 Jan;49(1):23-30.
8. Miner JR, Gray RO, Stephens D, Biros MH. Randomized clinical trial of propofol with and without alfentanil for deep procedural sedation in the emergency department. *Acad Emerg Med*. 2009 Sep;16(9):825-34.
9. Camu F, Vaniersbergh C. Pharmacology of systemic analgesics. *Best Pract Res Clin Anaesthesiol*. 2002;16:475-88.
10. Botero CA, Smith CE, Holbrook C, Chavez AM, Snow NJ, Hagen JF, et al. Total intravenous anesthesia with a propofol-ketamine combination during coronary artery surgery. *J Cardiothorac Vasc Anesth*. 2000 Aug;14(4):409-15.
11. Galinski M, Dolveck F, Combes X, Limoges V, Smail N, Pommier V, et al. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med*. 2007 May;25(4):385-90.
12. Messenger DW, Murray HE, Dungey PE, van Vlymen J, Sivilotti ML. Subdissociative-dose ketamine versus fentanyl for analgesia during propofol procedural sedation: a randomized clinical trial. *Acad Emerg Med*. 2008 Oct;15(10):877-86.
13. Erden IA, Pamuk AG, Akinci SB, Koseoglu A, Aypar U. Comparison of propofol-fentanyl with propofol-fentanyl-ketamine combination in pediatric patients undergoing interventional radiology procedures. *Paediatr Anaesth*. 2009 May;19(5):500-6.
14. Chiaretti A, Ruggiero A, Barone G, Antonelli A, Lazzareschi I, Genovese O, et al. Propofol/alfentanil and propofol/ketamine procedural sedation in children with acute lymphoblastic leukaemia: safety, efficacy and their correlation with pain neuromediator expression. *Eur J Cancer Care (Engl)*. 2010 Mar;19(2):212-20.
15. Arora S. Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: a review. *West J Emerg Med*. 2008 Jan;9(1):20-3.
16. Green SM. Research advances in procedural sedation and analgesia. *Ann Emerg Med*. 2007 Jan;49(1):31-6.
17. Trissel LA, Gilbert DL, Martinez JF. Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health Syst Pharm*. 1997 Jun 1;54(11):1287-92.
18. Sharieff GQ, Trocinski DR, Kanegaye JT, Fisher B, Harley JR. Ketamine-propofol combination sedation for fracture reduction in the pediatric emergency department. *Pediatr Emerg Care*. 2007 Dec;23(12):881-4.
19. Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). *Acad Emerg Med*. 2010 Feb;17(2):194-201.
20. Green SM, Krauss B. Procedural sedation terminology: moving beyond "conscious sedation". *Ann Emerg Med*. 2002 Apr;39(4):433-5.
21. Mourad M, El-Hamamsy M, Anwar M, Schwarz E. Low dose ketamine reduces sedative doses of propofol during ambulatory transoesophageal echocardiography. *Egypt J Anaesth*. 2004; 20:41-6.
22. Mohamed Daabiss, Medhat Elsherbiny and Rashed Alotibi. Assessment of different concentration of Ketofol in procedural operation. *BJMP* 2009;2(1) 27-31
23. Badrinath S, Avramov MN, Shadrack M, Witt TR, Ivankovich AD. The use of a ketamine-propofol combination during monitored anesthesia care. *Anesth Analg*. 2000 Apr;90(4):858-62.
24. da Silva PS, de Aguiar VE, Waisberg DR, Passos RM, Park MV. Use of ketofol for procedural sedation and analgesia in children with hematological diseases. *Pediatr Int*. 2011 Feb;53(1):62-7.
25. Akin A, Esmaoglu A, Tosun Z, Gulcu N, Aydogan H, Boyaci A. Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. *Int J Pediatr Otorhinolaryngol*. 2005 Nov;69(11):1541-5.

26. Tosun Z, Aksu R, Guler G, Esmaglu A, Akin A, Aslan D, et al. Propofol-ketamine vs propofol-fentanyl for sedation during pediatric upper gastrointestinal endoscopy. *Paediatr Anaesth*. 2007 Oct;17(10):983-8.
27. Chiaretti A, Ruggiero A, Barone G, Antonelli A, Lazzareschi I, Genovese O, et al. Propofol/alfentanil and propofol/ketamine procedural sedation in children with acute lymphoblastic leukaemia: safety, efficacy and their correlation with pain neuromediator expression. *Eur J Cancer Care (Engl)*. 2010 Mar;19(2):212-20.
28. Aouad MT, Moussa AR, Dagher CM, Muwakkit SA, Jabbour-Khoury SI, Zbeidy RA, et al. Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. *Acta Anaesthesiol Scand*. 2008 Apr;52(4):561-5.
29. Akin A, Esmaglu A, Tosun Z, Gulcu N, Aydogan H, Boyaci A. Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. *Int J Pediatr Otorhinolaryngol*. 2005 Nov;69(11):1541-5.
30. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007 Jan;49(1):23-30.
31. Green SM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation in children. *Ann Emerg Med*. 2004 Nov;44(5):460-71.
32. Akin A, Guler G, Esmaglu A, Bedirli N, Boyaci A. A comparison of fentanyl-propofol with a ketamine-propofol combination for sedation during endometrial biopsy. *J Clin Anesth*. 2005 May;17(3):187-90.
33. Nagata A, Nakao S, Miyamoto E, et al. Propofol inhibits ketamine-induced expression in the rat posterior cingulate cortex. *Anesth Analg* 1998;87:141620.
34. Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K, Sheppard RA. The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. *Anesth Analg*. 2001 Jun;92(6):1465-9.