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Retrospective evaluation of ketamine-propofol combination for procedural sedation in children undergoing biopsies

Biyopsi yapılan çocukların sedasyonunda ketofol propofol kombinasyonunun retrospektif incelenmesi

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ABSTRACT

The aim of this study is to evaluate the effectiveness and safety of an intravenous ketamine-propofol combination (ketofol) for procedural sedation in children undergoing biopsies. In this retrospective study, the data collected from patients' records included age, sex, weight, diagnosis, procedure length, time to sedation, total ketofol dose, recovery time, total sedation time, and adverse effects. A total of 80 patients (40 females and 40 males) received ketofol for sedation for biopsies performed over a 6-month period. The mean age of the patients was 7.4±4.6 years. The mean duration of the procedures was 14±3.6 minutes. The mean body weight of the patients and the average induction dose were 28.4±15.5 kg and 2±1.17 mg/kg, respectively. Patients recovered wrthin 13.9±5.8 minutes and the mean sedation time was 28.3±8.1 minutes. A total of 28 patients (35%) had adverse events, including nystagmus (n=20; 25%), transient diplopia (n=4; 5%), and unpleasant emergence reactions (n=4; 5%). None of the patients required an airway intervention or had hypotension or vomiting. Ketofol provided adequate sedation and patient immobility in children undergoing biopsies. We observed hemodynamic stability, satisfactory postoperative recovery profiles, without any clinically significant complications. Our data suggest that ketofol is an effective sedative agent that provides a safe procedural sedation in children undergoing biopsies.

Keywords: *Ketamine, propofol, sedation, pediatrics, biopsy*

ÖZ

Bu retrospektif çalışmada biyopsi yapılan çocuklarda prosedürel sedasyon için intravenöz ketamin-propofol kombinasyonun (ketofol) etkinliğini ve güvenilirliğini değerlendirmek amaçlanmıştır. Hasta kayıtlarından yaş, cinsiyet, tanı, işlem süresi, total ketofol dozu, derlenme zamanı, total sedasyon zamanı, ve yan etki verileri toplandı. Toplam 6 aylık süre içinde biyopsi sırasında sedasyon için 80 hastada (40 kadın ve 40 erkek) ketofol kullanıldığı görüldü. Bu hastaların ortalama yaşı 7,4±4,6 yıl, ortalama işlem süresi 14±3,6 dk. idi. Ortalama kiloları 28,4±15,5 kg, ortalama indüksiyon dozu ise 2±1,17 mg/kg idi. Hastalar ortalama 13,9±5,8 dk.'da derlendi. Total sedasyon zamanları ortalama 28,3±8,1 dk. idi. Yan etki 28 hastada (%35) gözlendi. Bu hastaların 20'sinde nistagmus (%25), 4'ünde geçici diplopi (%5), 4'ünde (%5) ajitasyon saptandı. Hiçbir hastada havayolu müdahalesi gerekmedi; hipotansiyon, kusma olmadı. Biz bu çalışmada ketofolün biyopsi sırasında tüm hastalarda yeterli sedasyon ve hareketsizlik sağladığını, hiçbir ciddi komplikasyon olmadan, hemodinamik stabilite ve tatmin edici derlenme sağladığını gözlemledik. Verilerimiz biyopsi yapılan çocuklarda ketofolün etkin ve güvenli sedasyon yaptığını göstermektedir.

Anahtar kelimeler: *Ketamin, propofol, sedasyon, çocuk, biyopsi*

INTRODUCTION

The number of diagnostic and therapeutic procedures outside the operating room has increased in recent years. Because most of these procedures are painful, and so children often require sedation[1,2]. The needed level of sedation for pediatric patients is generally a deep sedation in which they are more prone to respiratory depression and life- threatening hypoxia compared with adults[2]. Non-operating room

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anesthesia (NORA) is not so innocent when possible side effects such as hypothermia, pain, aspiration, apnea, and respiratory problems requiring airway/ventilation interventions are considered[3]. According to a report from the reviewed literature and the American Society of Anesthesiologists (ASA) Closed Claim database, inadequate oxygenation/ventilation is the most common event seen related to anesthesia given outside the operating room[4]. Therefore, the selection of appropriate medications is essential in procedural sedation[5]. Procedural sedation refers to the technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining his/her cardiorespiratory function[6]. Propofol is one of the most commonly used sedative-hypnotic agents for these procedures. However, large doses may be required to ensure patient immobility for painful procedures like biopsies, and these doses can result in cardiovascular and respiratory depression[7]. The combination of ketamine and propofol in the same syringe (ketofol) lowers the dosage requirements of each agent, decreases the incidence of adverse effects, and provides effective procedural sedation in emergency department settings[8]. The efficiency and safety of ketofol have also been reported in various procedures and in different suites[9-11]. In this study, we aimed to evaluate the effectiveness and safety of intravenous ketofol for procedural sedation in children undergoing biopsies.

MATERIAL and METHODS

This retrospective study was approved by the Clinical Research Ethical Committee of Ondokuz Mayis University. We included ASA physical status Class I and II patients who received ketofol for biopsy procedures in the interventional radiology suite. We excluded patients who received other anesthetic agents, who had incomplete anesthesia records, or who had premedication with midazolam before sedation. After placement of a peripheral catheter, the patients received intravenous ketofol (1:1 mixture of ketamine [10 mg/mL] and propofol [10 mg/mL] in a single syringe) in a bolus dose of 1 mg/kg followed by an additional dose of 0.5 mg/kg to achieve the targeted level of a Ramsay sedation score of 4. Data from January 2015 to July 2015 were collected from patients' records which included age, sex, weight, diagnosis, procedure length, time (in minutes) to reach Ramsay sedation score of 4 from the initial administration of the sedative (time to sedation), total ketofol dose, time elapsed from the end of the procedure up to fulfillment of the discharge criteria (recovery time), time from adequate sedation (Ramsay sedation score of 4) up to fulfillment of the discharge criteria (total sedation time), and adverse effects.

Statistical analyses were performed with SPSS 18.0 for Windows. Data were presented as mean±standard deviation (SD), as a median (min-max), and frequency (%). The Shapiro- Wilk test was used to analyze normal distribution assumptions of the quantitative outcomes. To compare two independent groups, we used Mann-Whitney U test for data with nonnormal distribution. The intragroup data within each of the three groups were compared with the paired-samples t-tests for normal data. Fisher's exact tests were used for comparisons of percentages. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 80 patients (40 females and 40 males) received ketofol for sedation for biopsies within the

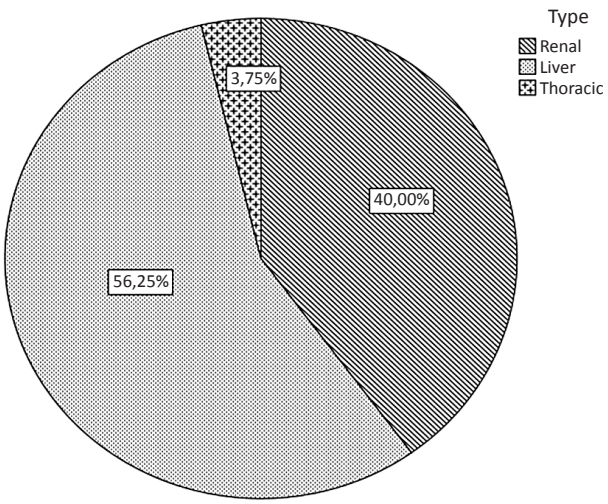

Figure 1. The distribution of the types of biopsies.

6-month period. All of the procedures were completed successfully, and all patients breathed spontaneously through an oxygen facemask without an artificial airway. There was no apnea or any respiratory problems that required airway/ventilation interventions throughout the procedures. The most common procedure was liver biopsy. The distribution of procedures can be seen in Figure 1.

The mean age of the patients was 7.4±4.6 years. While 9 patients (11.3%) were in ASA I, and 71 patients (88.8%) patients were in ASA II status. The mean length of the procedures was 14±3.6 minutes. The mean body weight of the patients and the mean induction dose were 28.4±15.5 kg and 2±1.17 mg/kg, respectively. Mean recovery, and total sedation times were 13.9±5.8 and 28.3±8.1 minutes, respectively (Table 1). There were significant differences in ASA I and II patients regarding recovery and total sedation times (Table 2). Median recovery times were 17 min (2-25 min), and 8 min (5-15 min) in ASA II, and ASA I patients, respectively (p=0.001). Similarly, median total sedation time was longer in ASA II patients (31 min [12-40 min]) than in ASA I patients (20 min [12-35 min]) (p=0.007). The heart rate at the beginning of the sedation was lower in ASA II than ASA I patients (98 bpm [60-130 bpm] vs. 108 bpm [99-121 bpm]) (p=0.038). However, there were no statistically significant differences between ASA I and II patients with respect to heart rates at the fifth and tenth minutes (Table 2). There were 28 patients (35%) who experienced adverse events as nystagmus (n=20; 25%), transient diplopia (n=4; 5%), and unpleasant arousal reactions (n=4; 5%). None of the patients required an airway intervention or had hypotension or vomiting.

Table 1. Demographic and sedation data of the patients (n=80).

	Frequency (%)	Mean±SD	Median (min-max)
Demographic			
Sex			
Male	40 (50)		
Female	40 (50)		
ASA			
I	9 (11.3)		
II	71 (88.8)		
Age (years)		7.3±4.6	6 (0.1-17)
Weight (kg)		28.4±15.5	25 (4.8-66)
Characteristics			
Procedure length		14±3.6	15 (5-25)
Total dose (mg/kg)		2±1.1	1.8 (0.7-9.3)
Time to sedation[a] (sec)		40±26.5	35 (10-180)
Time to recovery[b] (min)		13.9±5.8	15 (2-25)
Total sedation time[c] (min)		28.3±8.1	30.5 (12-40)
Respiratory rate (per minute)		23.8±3.4	23 (17-35)
Heart rate 0. (per min)		97.2±15.6	99 (60-130)
Heart rate 5. (per min)		97.8±16.7	99 (68-140)
Heart rate 10. (per min)		97.1±16.1	99 (69-140)
End-tidal CO_2 (mmHg)		29.6±4.5	31 (18-37)
SPO_2 (%)		98.7±2.5	99 (99-100)

[a]Time in minutes from initial administration of the sedative to the achievement of adequate sedation of the patient (Ramsay sedation score of 4)
[b]Time elapsed from the end of the procedure to meeting the discharge criteria
[c]Time from adequate sedation (Ramsay sedation score of 4) to meeting the discharge criteria

Table 2. Comparison of ASA I-II on the basis of recovery and total sedation times.

	ASA I*	ASA II*	P value
Recovery time (min)	8 (5–15)	20 (12-35)	0.001
Total sedation time (min)	17 (2-25)	31 (12-40)	0.007
Heart rate at 0 minutes (bpm)	108 (99-121)	98 (60-130)	0.038
Heart rate at 5 minutes (bpm)	107 (90-129)	98 (68-140)	0.103
Heart rate at 10 minutes (bpm)	101 (92-125)	98 (69-140)	0.118

** Data are medians (min-max)*

DISCUSSION

In the present study, the efficiency and safety of intravenous ketofol for procedural sedation in children undergoing biopsies were evaluated. Results of the present study demonstrated that the combination of ketamine and propofol provided adequate sedation and patient immobility in children undergoing biopsies. We observed hemodynamic stability, satisfactory postoperative recovery profiles, and lack of clinically significant complications.

Propofol is the most preferred agent in procedural sedation and has certain advantages such as having a fast sedative effect after intravenous administration, smooth sedation, and short duration of action,

antiemetic effect, and high patient satisfaction rates. However, it also has some disadvantages including respiratory depression and hypotension[12]. The first literature data concerning a ketamine-propofol combination was in the 1990s[13]. While recognizing the positive effect of propofol on unpleasant hallucinations after ketamine use, and the hemodynamic stability with this drug combination, ketofol usage has gained popularity in the NORA field[13-15]. What makes ketofol a popular anesthetic combination is its intriguing synergistic property in which ketamine balances the respiratory depression and hypotension effects of propofol. Similarly, propofol balances the vomiting and hallucinatory effects of ketamine. On the other side, adding ketamine to propofol can preclude an opioid requirement with its analgesic effects[16].

In a study investigating the use of ketamine-propofol combination in 100 female patients undergoing breast biopsies, the authors found a reduction in the rescue opioid requirement[17]. This reduction was dose dependent and increased in parallel with the increase in ketamine concentration added to the propofol. They used a ketamine-propofol infusion and also reported dose-dependent effects on nausea and vomiting, psychomimetic side effects (dreams, hallucination), visual disturbances (double vision, nystagmus), and a delayed recovery time. In our study, none of our patients experienced nausea and vomiting or hallucinations, however, some of them had diplopia and nystagmus. Lack of nausea and vomiting in our patients may be due to the different methods of using ketofol, and the duration of the procedures in our and the above-mentioned study (bolus vs. infusion, 13.9 vs. 50 min respectively). Ultimately, they concluded that ketamine may be a useful adjuvant to propofol sedation[17]. In another study, Willman et al.[18] evaluated the safety of an intravenous ketamine-propofol combination in the same syringe for sedation during primarily orthopedic procedures in the emergency room. In 114 patients, they reported unpleasant emergence in 2.6% of the patients, and the median recovery time was 15 minutes, which is in agreement with our findings. They also concluded that ketofol is effective and safe for procedural sedation in the emergency department.

Similar to our study, Erden et al.[9] hypothesized that adding ketamine would decrease the propofol/fentanyl-associated oxygen desaturation. This group compared propofol-fentanyl with a propofol fentanyl-ketamine combination in patients undergoing interventional radiologic procedures. They did not report any incident of apnea in anyone of their groups, which is in agreement with our findings. However, in the propofol-fentanyl-ketamine combination group, 10% of the patients had O_2 desaturation, which may have been due to the fentanyl added to the ketamine-propofol mixture[9]. Because none of our patients had O_2 desaturation with a pure ketamine-propofol mixture, we believe that an investigation is warranted to determine if there is a reason to add fentanyl to the ketamine-propofol combination. One may also argue the need for adding ketamine to propofol rather than using ketamine alone for procedural sedation. For better clarification of this issue, Shah et al.[19] investigated ketamine-propofol versus ketamine alone for orthopedic reduction procedures, and the data from their study suggested that a ketamine-propofol combination produced faster recovery times with higher satisfaction scores. In comparisons of ketamine-propofol combination with ketamine alone, or with propofol alone, the combination showed better analgesia and shorter recovery times in children undergoing lumbar punctures and bone marrow aspirations[20]. In a prospective pediatric case series, 219 patients underwent ketofol sedation for orthopedic procedures in the emergency department, and the authors reported effective procedural sedation and analgesia in all patients. These patients received ketamine-propofol as a mixture in the same syringe and had recovery times similar to ours (14 vs. 13.97 min, respectively)[8]. Similar results were also reported in a study investigating ketofol use for sedation in children undergoing bone marrow aspirations[10]. Although its known that ASA physical status is a predictor of postoperative outcomes[21], exploring how the recovery and total sedation times have been effected by ASA scores are potential questions to be investigated in future studies.

A limitation of this study is that we evaluated ketofol usage for pediatric procedural sedation retrospectively. While there are many sedatives being used for procedural sedation, and different concentration ratio regimens for ketamine-propofol, there is a need to compare these different techniques prospectively with respect to recovery times, total sedation times, and adverse effects.

In summary, our data suggest that ketofol is an effective sedative agent that provides a safe procedural sedation in children undergoing biopsies.

REFERENCES

1. Havidich JE, Cravero JP. The current status of procedural sedation for pediatric patients in out-of-operating room locations. *Curr Opin Anaesthesiol* 2012;25:453-60. http://dx.doi.org/10.1097/ACO.0b013e32835562d8
2. Cravero JP, Blike GT. Pediatric anesthesia in the nonoperating room setting. *Curr Opin Anaesthesiol* 2006;19:443-9. http://dx.doi.org/10.1097/01.aco.0000236147.83364.99
3. Missant C, Van de Velde M. Morbidity and mortality related to anaesthesia outside the operating room. *Curr Opin Anaesthesiol* 2004;17:323-7. http://dx.doi.org/10.1097/01.aco.0000137091.75602.34
4. Robbertze R, Posner KL, Domino KB. Closed claims review of anesthesia for procedures outside the operating room. *Curr Opin Anaesthesiol* 2006;19:436-42. http://dx.doi.org/10.1097/01.aco.0000236146.46346.fe
5. Tobias JD, Leder M. Procedural sedation: A review of sedative agents, monitoring, and management of complications. *Saudi J Anaesth* 2011;5:395-410. http://dx.doi.org/10.4103/1658-354X.87270
6. Godwin SA, Caro DA, Wolf SJ, et al. Clinical policy: Procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2005;45:177-96. http://dx.doi.org/10.1016/j.annemergmed.2004.11.002
7. Singh R, Batra YK, Bharti N, et al. Comparison of propofol versus propofol-ketamine combination for sedation during spinal anesthesia in children: randomized clinical trial of efficacy and safety. *Paediatr Anaesth* 2010;20:439-44. http://dx.doi.org/10.1111/j.1460-9592.2010.03286.x
8. 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;17:194-201. http://dx.doi.org/10.1111/j.1553-2712.2009.00646.x
9. Erden IA, Pamuk AG, Akinci SB, et al. Comparison of propofol-fentanyl with propofol-fentanyl-ketamine combination in pediatric patients undergoing interventional radiology procedures. *Paediatr Anaesth* 2009;19:500-6. http://dx.doi.org/10.1111/j.1460-9592.2009.02971.x
10. da Silva PSL, de Aguiar VE, Waisberg DR, et al. Use of ketofol for procedural sedation and analgesia in children with hematological diseases. *Pediatr Int* 2011;53:62-7. http://dx.doi.org/10.1111/j.1442-200X.2010.03200.x
11. Heilbrunn BR, Chang TP, Liu DR. A retrospective comparison of ketamine dosing regimens for pediatric procedural sedation. *Eur J Emerg Med* 2015;22:111-6. http://dx.doi.org/10.1097/MEJ.0000000000000127
12. Krauss B, Green SM. Procedural sedation and analgesia in children. *Lancet* 2006;367:766-80. http://dx.doi.org/10.1016/S0140-6736(06)68230-5
13. Alletag MJ, Auerbach MA, Baum CR. Ketamine, propofol, and ketofol use for pediatric sedation. *Pediatr Emerg Care* 2012;28:1391-5; quiz 6-8. http://dx.doi.org/10.1097/PEC.0b013e318276fde2
14. Friedberg BL. Hypnotic doses of propofol block ketamine-induced hallucinations. *Plast Reconstr Surg* 1993;91:196-7. http://dx.doi.org/10.1097/00006534-199301000-00047
15. Guit JB, Koning HM, Coster ML, et al. Ketamine as analgesic for total intravenous anaesthesia with propofol. *Anaesthesia* 1991;46:24-7. http://dx.doi.org/10.1111/j.1365-2044.1991.tb09308.x
16. Green SM, Andolfatto G, Krauss B. Ketofol for procedural sedation? Pro and con. *Ann Emerg Med* 2011;57:444-8. http://dx.doi.org/10.1016/j.annemergmed.2010.12.009
17. Badrinath S, Avramov MN, Shadrick M, et al. The use of a ketamine-propofol combination during monitored anesthesia care. *Anesth Analg* 2000;90:858-62. http://dx.doi.org/10.1213/00000539-200004000-00016
18. 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;49:23-30. http://dx.doi.org/10.1016/j.annemergmed.2006.08.002
19. Shah A, Mosdossy G, McLeod S, et al. A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Ann Emerg Med* 2011;57:425-33 e2. http://dx.doi.org/10.1016/j.annemergmed.2010.08.032
20. Chiaretti A, Ruggiero A, Barbi E, et al. Comparison of propofol versus propofol-ketamine combination in pediatric oncologic procedures performed by non-anesthesiologists. *Pediatr Blood Cancer* 2011;57:1163-7. http://dx.doi.org/10.1002/pbc.23170
21. Magi E. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth* 1997;78:228. http://dx.doi.org/10.1093/bja/78.2.228