https://doi.org/10.31925/farmacia.2023.5.11 **ORIGINAL ARTICLE**

THE IMPORTANCE OF ANALGO-SEDATION IN THE PATIENT WITH SERIOUS PELVIC AND SPINE TRAUMA DURING TRANSPORT

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Abstract

This prospective, randomised study aimed to assess the efficacy of ketamine/propofol (K/P) compared to the commonly used fentanyl/midazolam (F/M) combination in providing analgesia for patients with severe pelvic and spinal trauma. The study, conducted over 30 months on 154 patients, found that the K/P group experienced significantly lower perceived pain levels, as measured on the numerical pain scale, when compared to the F/M group ($p < 0.0001$). Additionally, patients in the K/P group achieved adequate sedation with an average Ramsay scale score of 3.1, while the F/M group had a more profound sedation with a score of 5.5 ($p < 0.0001$). Furthermore, the study demonstrated that analgesia with K/P significantly improved the physiological severity score (PSS) ($p < 0.0001$) and resulted in a notably lower incidence of oxygen desaturation, with only one patient experiencing this in the K/P group compared to 16 patients in the F/M group ($p = 0.0003$). These findings suggest that co-administration of low-dose ketamine and propofol provides safe and effective sedation and analgesia, both in the emergency department and pre-hospital settings. The study highlights the importance of adequate pain management in severe trauma cases and emphasizes the potential advantages of using the K/P combination over F/M, particularly due to the reduced risk of oxygen desaturation and the more moderate level of sedation achieved with K/P. These results underscore the potential clinical utility of this approach in improving the overall care and outcomes of patients with severe pelvic and spinal trauma.

Rezumat

Acest studiu prospectiv, randomizat, a avut ca scop evaluarea eficacității combinației ketamină/propofol (K/P) în comparație cu fentanil/midazolam (F/M) pentru inducerea analgeziei la pacienții cu traume severe ale pelvisului și coloanei vertebrale. Studiul, efectuat pe o perioadă de 30 de luni la 154 de pacienți, a constatat că grupul K/P a prezentat niveluri semnificativ mai scăzute ale durerii percepute, măsurate pe scara numerică a durerii, comparativ cu grupul F/M ($p < 0,0001$). În plus, pacienții din grupul K/P au obținut o sedare adecvată, cu un scor mediu pe scara Ramsay de 3,1, în timp ce grupul F/M a obținut un scor de sedare mai profundă de 5,5 ($p < 0,0001$). În plus, studiul a demonstrat că analgezicele K/P au îmbunătățit semnificativ scorul de severitate fiziologică (PSS) ($p < 0,0001$) și au dus la o incidență mai scăzută a pacienților care au avut nevoie de oxigen suplimentar, doar un singur pacient din grupul K/P comparativ cu 16 pacienți din grupul F/M ($p = 0,0003$). Aceste constatări sugerează că administrarea concomitentă în doze mici de ketamină/propofol produce o sedare și o analgezie mai sigure și mai eficiente, atât în departamentul de urgență, cât și în îngrijirea prespitalicească. Studiul evidențiază importanța managementului adecvat al durerii în cazurile de traumatisme severe și subliniază potențialele avantajele ale utilizării combinației K/P în comparație cu F/M, în special datorită riscului redus de desaturare a oxigenului și a nivelului mai scăzut de sedare obținut cu K/M. Aceste rezultate subliniază utilitatea clinică potențială a acestei abordări în îmbunătățirea îngrijirii generale și a rezultatelor pacienților cu traumatisme severe ale pelvisului și ale coloanei vertebrale.

Keywords: severe pelvic and spine trauma, ketamine/propofol, fentanyl/midazolam, analgesia, sedation

Introduction

Recent changes in trauma treatment include an emphasis on pain treatment to decrease the potent inflammatory response that results in hypercoagulability, organ dysfunction, systemic inflammatory response, lung injury, brain injury, depression and post-traumatic stress disorder [1].

Propofol is classified as a sedative-hypnotic medication characterised by its rapid onset and short duration of action [2]. Propofol has some disadvantages, such as a painful infusion, transient cognitive dysfunction and cardiovascular and respiratory depression. It is also not analgesic [3-5].

Ketamine is a phencyclidine derivative with dissociative, sedative, analgesic and amnestic properties that preserve muscle tone and protect airway reflexes and spontaneous breathing [6]. Associated with propofol, it prevents pain during propofol infusion [7-8], and counteracts the hemodynamic, cardiovascular and respiratory depression of propofol. Side effects such as dysphoria,

vomiting, or laryngospasm may be observed [9-11] when used alone. The combination of ketamine and propofol decreases dose-dependent side effects [12]. The effectiveness of ketamine and propofol administered as a bolus has been established in several settings, including the operating room [13], the emergency department for rapid sequence induction of orotracheal intubation, and for analgesia during painful procedures [14-16].

The London Helicopter Emergency Medical Service reported using ketamine for procedural analgesia and sedation. It has been concluded that ketamine is safe when used by physicians in pre-hospital trauma care [17]. There are few scientific studies on the pre-hospital use of analgesics [18], and under-treatment of pain is frequently reported [19].

In Romania, combining an opioid with a benzodiazepine is frequently used for the analgo-sedation of critical patients, the most commonly used combination being fentanyl with midazolam. Hence, there is a lack of scientific studies that have provided conclusive evidence on the efficacy of the ketamine/propofol combination in the treatment of critical trauma patients.

Based on the available data, a prospective, randomised, interventional trial was undertaken to investigate the potential benefits of using a combination of ketamine and propofol compared to the more frequently employed midazolam/fentanyl combination in patients with severe pelvic and spine trauma. The study aimed to assess the significance of analgo-sedation in this patient population, which typically experiences hemodynamic instability. The study was approved by the hospital's ethics committee, and written informed consent was obtained from all patients.

Materials and Methods

Study design

The research conducted in this study encompasses a duration of 30 months, specifically from September 2019 to February 2022. The study population consisted of 154 patients, who were randomly assigned to two groups in a 1:1 ratio. The first group, referred to as the Ketamine/Propofol group, comprised 77 patients, while the second group, known as the Fentanyl/ Midazolam group, also consisted of 77 patients. In this context, rigorous inclusion and exclusion criteria were established to ensure the appropriate selection of participants. The inclusion criteria encompassed patients who exhibited severe pelvic trauma and spine trauma and were aged 18 years or older.

On the other hand, exclusion criteria were methodically defined in order to exclude individuals who did not satisfy the predetermined criteria. Patients with an American Society of Anaesthesiology (ASA) physical status score of 3 or higher were excluded. Additionally, individuals with a documented history of adverse reactions to specific medications, namely ketamine, propofol, midazolam, fentanyl, or egg products, were ineligible for participation. The presence of pregnancy in potential participants was another exclusion criterion. Moreover, individuals with concurrent brain trauma associated with pelvic or spinal trauma were also excluded.

The study employed specific dosage regimens to administer the selected medications to eligible participants. The dosages were as follows: Ketamine was administered in a range of 0.125 to 0.5 mg/kg in combination with propofol at a dosage of 0.5 mg/kg. Additionally, fentanyl was administered at a dosage range of 1 to 2 μg/kg, accompanied by midazolam at a dosage of 0.1 mg/kg. The medication for continuous intravenous infusion was prepared with a 50 mL syringe with 500 mg ketamine (10 mg/1 mL) and a 50 mL syringe with 500 mg propofol (10 mg/1 mL). No patient became hypotensive at this dose. Midazolam was provided at a concentration of 1 mg/1 mL, and fentanyl at 20 μg/1 mL. For the K/P group, patients received a combination of 0.2 mg/kg of ketamine and 0.5 mg/kg of propofol. In contrast, the F/M group received 1 μg/kg of fentanyl and 0.1 mg/kg of midazolam. The following parameters were evaluated: pain intensity using the numerical rating scale (NRS) (Figure 1), pulse rate, respiratory rate, oxygen saturation, systolic blood pressure and state of consciousness using the Glasgow Coma Score (GCS) (Table I).

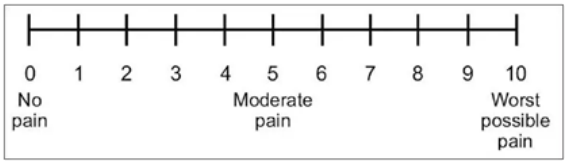

Figure 1.
Numerical rating scale (NRS)

Table I
Glasgow Coma Score

Eye(s) opening	Spontaneous	4
	To speech	3
	To pain	2
	No response	1
Verbal response	Oriented to time, place, person	5
	Confused/disorientated	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localised pain	5
	Flexion withdraws from pain	4
	Abnormal flexion	3
	Abnormal extension	2
	No response	1
Best response		15
Comatose patient		8 or less
Totally unresponsive		3

The primary outcome variable was a change in the Physiological Severity Score (PSS) and pain severity (Table II). The level of sedation was assessed by the Ramsay Sedation Scores (RSS) (Table III).

Table II

Physiological Severity Score (PSS)

	0 points	**1 point**	**2 points**	**3 points**	**4 points**
Respiratory rate (breaths/minute)	No breathing	< 10	> 35	25 - 35	10 - 24
Systolic blood pressure (mmHg)	No pulse	< 50	50 - 69	70 - 90	> 90
Level of consciousness	No response	Pain response	Sound response	Confused	Normal

Table III

Ramsay Sedation Score – RSS [20-21]

1	The patient is anxious, agitated and/or restless
2	The patient is cooperative, oriented and tranquil
3	The patient responds to commands only
4	The patient sleeps and exhibits brisk response to light glabellar tap or loud auditory stimulus
5	The patient sleeps and exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	The patient exhibits no response

This score is used in anaesthesiology and intensive care, having a score between 1 - 6 points.

Statistical analysis methods

To develop a consistent and relevant statistical study, the methods of medical statistics in the Anglo-Saxon specialised literature were studied. All information was stored and processed using the Microsoft® Excel® 2010 programme (Microsoft® Corporation, USA), constituting the database of the statistical study.

In our study, we employed statistical analysis methods, including the t-test for comparing means and the test for comparing proportions. These analyses were conducted using the medical statistics application MedCalc® version 12.2.1.0, developed by MedCalc® Software in Mariakerke, Belgium. A p-value less than 0.05 indicates a statistically significant difference between the groups under study.

Results and Discussion

Analysing the clinical characteristics after initiation of analgo-sedation, the results of the study show a more significant decrease in pulse rate in patients who received analgesia with fentanyl/midazolam compared to those who received ketamine/propofol, with a statistically significant difference ($p < 0.0001$) (Table IV). However, no patient had hypotension between the two groups.

Oxygen desaturation occurred in 16 cases in the fentanyl/midazolam group and at one point in the ketamine/propofol group, the latter causing apnoea, with a statistically significant difference ($p = 0.0003$). They required tank-mask ventilation, but none were intubated (Table IV and Table V).

Perceived pain, using the Numerical Pain Rating Scale, was significantly lower in the ketamine/propofol group compared to the fentanyl/midazolam group ($p < 0.0001$) (Table IV).

According to the Ramsay scale, patients had adequate sedation on average at 3.5 (2 - 4) points in the ketamine/propofol group, compared to 5.5 (5 - 6) points, where sedation was more profound, with a significant difference between groups ($p < 0.0001$). Analgesia showed a substantial improvement in PSS (Physiological Severity Score) ($p < 0.0001$) (Table IV).

Table IV

Clinical characteristics after initiation of analgo-sedation

Changes in the value of the parameters after analgo-sedation (mean, range, SD)	**(K/P, n = 77)**	**(F/M, n = 77)**	**p†**
Pulse rate (b/min)	6.5 (4 - 9; 1.7)	9.35 (4 - 15; 3.45)	p < 0.0001*
TAS mmHg	7.17 (4 - 10; 2.15)	7.78 (4 – 12; 2.76)	p = 0.1281*
Respiratory rate (breaths/minute)	0.9 (0 - 2; 0.9)	0.7 (0 – 2; 0.8)	p = 0.1471*
Number of patients experiencing a decrease in oxygen saturation < 90%	1 (1.30%)	16 (20.78%)	p = 0.0003**
Patients requiring mask and balloon ventilation	1 (1.30%)	16 (20.78%)	p = 0.0003**
Mean decrease in pain scale	0.5 (0 - 1; 0.5)	3,3 (1 - 6; 1.7)	p < 0.0001*
Ramsay Sedation Score - RSS	3.1 (2 - 4; 0,9)	5.5 (5 - 6; 0.5)	p < 0.0001*
Physiological Severity Score (PSS) before analgo-sedation	9.97 (9 - 11; 0.81)	7.21 (4 - 11; 2.26)	p < 0.0001*
Physiological Severity Score (PSS) after analgo-sedation	1.4897 (1.4 - 1.6; 0.0567)	1.4242 (1.2 - 1.6; 0.1119)	p < 0.0001*

*Comparison of means test2, **Comparison of proportions test, †p < 0.05 proves a statistically significant difference between the studied groups

Table V

Comparison between the adverse effects and the medication used

	(K/P, n = 77)	**(F/M, n = 77)**	**p†**
No adverse effects	65 (84.41%)	59 (76.62%)	p = 0.3092*
Adverse effects	12 (15.58%)	18 (23.37%)	p = 0.3091*
Agitation	5 (6.49%)	0	p = 0.0691*
Involuntary movements	3 (3.89%)	0	p = 0.2443*
Apnoea	1 (1.30%)	0	p = 0.9992*
Oxygen desaturation	1 (1.30%)	16 (20.78%)	p = 0.0003*
Cough	1 (1.30%)	0	p = 0.9992*
Bradycardia	0	1 (1.30%)	p = 0.9992*
Hiccup	0	1 (1.30%)	p = 0.9992*
Vertigo	1 (1.30%)	0	p = 0.9992*

**Comparison of proportions test, †p < 0,05 proves a statistically significant difference between the studied groups

In terms of adverse effects, no statistically significant difference was observed between the two groups of patients overall (p = 0.3091). Oxygen desaturation was the only negative impact, with a statistically significant difference between the two groups (p = 0.0003) (Table V).

Five patients in the ketamine/propofol group developed agitation, but only one required intravenous midazolam 0.025 mg/kg with prompt episode resolution. Three patients in the ketamine/propofol group had involuntary movements. One patient (1.30%) in the ketamine/ propofol group presented a short, self-limited cough episode immediately after medication administration without statistical significance. Other adverse effects were bradycardia and hiccups, which resolved spontaneously in the fentanyl/midazolam group, and one patient in the ketamine/propofol group developed vertigo but without statistical significance (Table V).

Although propofol has been shown to have adverse effects on hemodynamic and respiratory parameters, our study showed that there were no cases of hypotension, bradycardia, or hypoxia requiring invasive management. In the fentanyl/midazolam group, the rate of oxygen desaturation ($SpaO_2$ < 90%) was 20.78%, and in the ketamine/propofol group, it was 1.30%, probably due to the patency of the airways and preservation of muscle tone by the use of ketamine and the use of a lower dose of propofol, a result found in the existing literature [22]. In previous studies, hypoxia secondary to propofol occurred in only about 5% of patients, and respiratory support by mask ventilation was required in 0.8% [23-24]. The hypoxia rate recorded in our study is consistent with the findings reported in the existing literature on sedation using ketamine/propofol. Akin *et al*. showed that the addition of low-dose ketamine to propofol maintained mean arterial pressure and reduced the risk of respiratory depression [25-26].

Goh *et al*. found that ketamine/propofol optimise hemodynamic and minimise apnoea [27]. Green *et al*. found a significant incidence of mild transient laryngospasm (8.2%) in a group of children sedated for gastroscopy with ketamine as a single agent at a total dose of 1.3 mg/kg [28]. Miner *et al*. detected a higher rate of subclinical respiratory depression in patients undergoing procedural sedation with ketamine for painful procedures in the emergency department than propofol. However, there was no difference in the rate of clinical interventions related to respiratory depression between groups [18]. Risk factors predicting respiratory and respiratory ketamine-related events are high intravenous doses and the use of co-administered anticholinergics or benzodiazepines [29].

Agitation or delirium is more common in adults than children and is an adverse effect of ketamine [30-31]. Five patients (6.49%) in our study developed agitation; only one was severe enough to be treated with midazolam. In a study of 1,022 paediatric and adolescent patients, Green *et al*. [12] reported the occurrence of mild agitation in 17.6% and moderate/severe fever in 1.6% of patients. Chudnofsky *et al*. described the phenomenon of agitation in 50% of adults [32]. Compared with these studies, our results suggest that ketamine/propofol combination is associated with a lower agitation rate than ketamine alone [33]. The effect is self-limiting, and the treatment remains symptomatic, relying on benzodiazepines and/or antipsychotics (*e.g.*, haloperidol) [34-35]. Concomitant midazolam has been shown to reduce the incidence of recovery agitation after procedural ketamine analgesia in adults in the emergency department. However, this is not a consistent finding across studies [36-37]. Nagata *et al*. and Mortero *et al*. suggested that ketamine in sedative doses is associated with electroencephalographic activation [2, 38]. The excitatory effects of ketamine may partially antagonise the sedative effects of propofol. In addition, low doses of ketamine increase thalamic sensory output and excitation. This could be a dose-dependent interaction of ketamine with a central nervous system depressant such as propofol [39].

Ketamine has the potential to induce emesis, while lower doses of propofol are reported to possess anti-emetic properties through the antagonism of dopamine D2 receptors. These lower dosages have been observed to effectively alleviate refractory nausea and vomiting among patients undergoing chemotherapy [40-41].

Early adolescence is the peak age for ketamine-associated emesis, and its rate is higher with intramuscular administration and unusually high intravenous doses [42]. In this study, there were not observed any nausea or vomiting as adverse effects.

In the present investigation, the assessment of experienced pain was conducted using the numerical pain scale. Notably, the ketamine/propofol group exhibited considerably lower levels of perceived pain compared to the fentanyl/midazolam group. This observation aligns with previous research findings as documented in the literature [43]. The administration of propofol independently has been observed to be linked to a reduction in systemic blood pressure. On the other hand, the administration of ketamine has been found to result in a notable increase in systolic blood pressure, which can be attributed to the stimulation of the sympathetic nervous system and concurrent moderate elevations in heart rate and systolic blood pressure. Ketamine does not affect breathing or laryngeal reflexes; under ketamine analgesia, patients breathe spontaneously and maintain airway control [44].

The existing literature also confirms etomidate's use in a rapid sequence of anaesthetic induction therapy in critical, hemodynamically unstable patients. However, its long-term use for sedation causes adrenal insufficiency and the aggravation of SIRS and sepsis, increasing the mortality rate. In the present study, we chose to use propofol as a sedative-hypnotic.

Conclusions

Concomitant administration of low-dose ketamine and propofol provided adequate sedation and analgesia with a lower oxygen desaturation than the fentanyl/midazolam combination, which has a deeper level of sedation and analgesia according to the Ramsay score, making it a safe and valuable technique in both the emergency department and in the prehospital. As with all procedural sedation and analgesia regimens, adverse effects are possible, and therefore adequate monitoring and the ability to intervene with cardio-respiratory support remain essential.

Conflict of interest

The authors declare no conflict of interest.

References

1. Malchow RJ, Black IH, The evolution of pain management in the critically ill trauma patient: emerging concepts from the global war on terrorism. *Crit Care Med.*, 2008; 36(7 Suppl): S346-S357.
2. Camu F, Vanlersberghe C, Pharmacology of systemic analgesics. *Best Pract Res Clin Anaesthesiol.*, 2002; 16: 475-488.
3. Mortero RF, Clark LD, Tolan MM, Metz RJ, Tsueda K, Sheppard K, The effects of small-dose ketamine on propofol sedation: respiration, postoperative mood, perception, cognition, and pain. *Anesth Analg.*, 2001; 92: 1465-1469.
4. WallsR, MurphyMF (eds.), *Manual of Emergency Airway Management*. Philadelphia, PA: Lippincott Williams & Wilkins, 2004.
5. 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.
6. Liang Y, Yuan J, Weng D, Huang Q, Cai S, Zhan J, Influence of dexmedetomidine on clinical efficacy of general anesthesia and stress response in children. *Farmacia*, 2022; 70(1): 138-143.
7. Short SM, Aun CS, Haemodynamic effects of propofol in children. *Anaesthesia*, 1991; 46: 783-785.
8. Hug CC Jr, McLeskey CH, Nahrwold ML, Roizen MF, Stanley TH, Thisted RA, Walawander CA, White PF, Apfelbaum JL, Grasela TH, Hemodynamic effects of propofol: data from over 25,000 patients. *Anesth Analg.*, 1993; 77(4 Suppl): S21-S29.
9. Bassett KE, Anderson JL, Pribble CG, Guenther E, Propofol for procedural sedation in children in the emergency department. *Ann Emerg Med.*, 2003; 42: 773-782.
10. Green SM, Krauss B, The semantics of ketamine [editorial]. *Ann Emerg Med.*, 2000; 39: 480-482.
11. Liu J, Wang H, Zhao X, Li L, Xia H, Liu Y, The effect of propofol on the proliferation of nephroblastoma cells and the underlying mechanism. *Farmacia*, 2022; 70(2): 325-330.
12. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP, Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology*, 1998; 88: 82-88.
13. Green SM, Rothrock SG, Lynch EL, Ho M, Harris T, Hestdalen R, Hopkins GA, Garrett W, Westcott K, Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. *Ann Emerg Med.*, 1998; 31(6): 688-697.
14. Suzuki S, Masamune T, Nonaka A, Kumazawa T, Pre-treatment with ketamine reduces incidence and severity of pain on propofol injection. *Masui.*, 2002; 51: 140-143, (available in Japanese).
15. Tan CH, Onsiong MK, Kua SW, The effect of ketamine pretreatment on propofol injection pain in 100 women. *Anaesthesia*, 1998; 53: 302-305.
16. Amir Nejati MD, Reza Shariat Moharari MD, Haleh Ashraf MD, Ali Labaf MD, Keihan Golshani MD, Ketamine/Propofol *Versus* Midazolam/Fentanyl for Procedural Sedation and Analgesia in the Emergency Department: A Randomized, Prospective, Double-Blind Trial. *Acad Emerg Med.*, 2011, 18(8): 800-806.
17. Bredmose PP, Lockey DJ, Grier G, Watts B, Davies G, Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J.*, 2009; 26(1): 62-64.
18. Park CL, Roberts DE, Aldington DJ, Moore RA, Prehospital analgesia: systematic review of evidence. *J R Army Med Corps.*, 2010; 156(4 Suppl 1): 295-300.
19. Alonso-Serra HM, Wesley K, National Association of EMS Physicians Standards and Clinical Practices Committee. Prehospital pain management. *Prehosp Emerg Care.*, 2003; 7(4): 482-488.

20. Suzuki S, Masamune T, Nonaka A, Kumazawa T, Pre-treatment with ketamine reduces incidence and severity of pain on propofol injection. *Masui*, 2002; 51: 140-143, (available in Japanese).
21. Ramsay MA, Savege TM, Simpson BR, Goodwin R, Controlled sedation with alphaxalone-alphadolone. *Br Med J.*, 1974; 2: 656-659.
22. Miner JR, Gray RO, Bahr J, Patel R, McGill JW, Randomized clinical trial of propofol versus ketamine for procedural sedation in the emergency department. *Acad Emerg Med.*, 2010; 17: 604-611.
23. Guenther EG, Pribble CG, Junkins EP Jr, Kadish HA, Bassett KE, Nelson DS, Propofol sedation by emergency physicians for elective pediatric outpatient procedures. *Ann Emerg Med.*, 2003; 42: 783-91.
24. Roback MG, Wathen JE, Bajaj L, Bothner JP, Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. *Acad Emerg Med.*, 2005; 12: 508-513.
25. Akin A, Esmaoglu A, Guler G, Demircioglu R, Narin N, Boyaci A, Propofol and propofol-ketamine in pediatric patients undergoing cardiac catheterization. *Pediatr Cardiol.*, 2005; 26: 553-557.
26. 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; 69: 1541-1545.
27. Goh PK, Chiu CL, Wang CY, Chan YK, Loo PL, Randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol saline on haemodynamics and laryngeal mask airway insertion conditions. *Anaesth Intensive Care.*, 2005; 33: 223-228.
28. Green SM, Klooster M, Harris T, Lynch EL, Rothrock SG, Ketamine sedation for pediatric gastroenterology procedures. *J Pediatr Gastroenterol Nutr.*, 2001; 32: 26-33.
29. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, McKee M, Weiss M, Pitetti RD, Hostetler MA, Wathen JE, Treston G, Garcia Pena BM, Gerber AC, JD Losek, Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med.*, 2009; 54: 158-168.
30. Green SM, Krauss B, Clinical practice guideline for emergency department ketamine dissociative sedation in children. *Ann Emerg Med.*, 2004; 44: 460-471.
31. Green SM, Sherwin TS, Incidence and severity of recovery agitation after ketamine sedation in young adults. *Am J Emerg Med.*, 2005; 23: 142-144.
32. Chudnofsky C, Weber J, Stoyanoff P, A combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department patients. *Acad Emerg Med.*, 2000; 7: 228-235.
33. Burns SM, Delirium during emergence from anesthesia: a case study. *Crit Care Nurse.*, 2003; 23: 66-69.
34. Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B, Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med.*, 2000; 35: 229-238.
35. Grace RF, The effect of variable-dose diazepam on dreaming and emergence phenomena in 400 cases of ketamine-fentanyl anaesthesia. *Anaesthesia*, 2003; 58: 904-910.
36. Sener S, Eken C, Schultz CH, Serinken M, Ozsarac M, Ketamine 971it hand without midazolam for emergency department sedation in adults: a randomized controlled trial. *Ann Emerg Med.*, 2011; 57: 109-114.
37. Wathen JE, Roback MG, Mackenzie T, Bothner JP, Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. *Ann Emerg Med.*, 2000; 36: 579-588.
38. Nagata A, Nakao S, Miyamoto E, Inada T, Tooyama I, Kimura H, Shingu K, Propofol inhibits ketamine-induced c-fos expression in the rat posterior cingulate cortex. *Anesth Analg.*, 1998; 87(6): 1416-1420.
39. Tomoda K, Shingu K, Osawa M, Murakawa M, Mori K, Comparison of CNS effects of propofol and thiopentone in cats. *Br J Anaesth.*, 1993; 71: 383-387.
40. Green SM, Johnson NE, Ketamine sedation for pediatric procedures. Part 2. Review and implications. *Ann Emerg Med.*, 1990; 19: 1033-1046.
41. Smith I, White PF, Nathanson M, Gouldson R, Propofol: an update on its clinical use. *Anesthesiology*, 1994; 81: 1005-1043.
42. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, McKee M, Weiss M, Pitetti RD, Hostetler MA, Wathen JE, Treston G, Garcia Pena BM, Gerber AC, JD Losek, Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med.*, 2009; 54: 171-180.
43. 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.
44. Strayer RJ, Nelson LS, Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med.*, 2008; 26(9): 985-1028.