Int J Clin Exp Med 2013;6(7):576-582
www.ijcem.com /ISSN:1940-5901/IJCEM1306004

*Original Article*

# Sedoanalgesia in pediatric daily surgery

Aybars Ozkan[1], Mesut Okur[2], Murat Kaya[1], Ertugrul Kaya[3], Adem Kucuk[4], Mesut Erbas[5], Leyla Kutlucan[6], Leyla Sahan[7]

*Departments of [1]Pediatric Surgery, [2]Pediatrics, [3]Pharmacology, School of Medicine, University of Duzce, Duzce, Turkey; Departments of [4]Pediatric Surgery, [5]Anesthesiology, School of Medicine, Canakkale On Sekiz Mart University, Canakkale, Turkey; [6]Department of Anesthesiology, State Hospital of Duzce, Duzce, Turkey; [7]Department of Anesthesiology, State Hospital of Isparta, Isparta, Turkey*

Received June 9, 2013; Accepted June 24, 2013; Epub August 1, 2013; Published August 15, 2013

**Abstract:** Purpose: The present report was focused on clinical advantages of sedoanalgesia in the pediatric outpatient surgical cases. Method: Sedoanalgesia has been used to sedate patients for a variety of pediatric procedures in our department between 2007 and 2010. This is a retrospective review of 2720 pediatric patients given ketamine for sedation with midazolam premedication. Ketamine was given intravenously (1-2 mg/kg) together with atropine (0.02 mg/kg) and midazolam (0.1 mg/kg) + a local infiltration anesthetic 2 mg/kg 0.5% bupivacaine hydrochloride. Result: Median age of the patients included in the study was 5.76 ± 2.12 (0-16 years). The main indications for ketamine include circumcision (69%), inguinal pathologies (inguinal hernia (17%), orchidopexy (2.68%), hydrocele (3.38%), hypospadias (1.94%), urethral fistula repair (0.33%), urethral dilatation (0.25%), and other conditions. All of our patients were discharged home well. In this regard, we have the largest group of patients ever given ketamine. Conclusion: Sedoanalgesia might be used as a quite effective method for daily surgical procedures in children.

**Keywords:** Child, ketamine, pediatric surgical procedures, sedoanalgesia

## Introduction

The outpatient elective operations are performed today more than ever before. Sedoanalgesia with local anesthesia is the most-preferred method in the outpatient elective operations [1]. Local anesthesia provides intraoperative anesthesia and postoperative analgesia in outpatient pediatric surgery, in particular for circumcision patients [2]. Bupivacaine, a generally preferred local anesthetic in nerve blocks, starts its analgesic effects in five minutes after administration, and serves about six to eight hours. This agent should be given with caution due to its significant side effects, including cardiotoxicity and neurotoxicity [3, 4].

Ketamine in analgesia and procedural sedation, for many diagnostic and therapeutic procedures, is supposed to be appropriate, particularly in children [5]. Ketamine analgesia is essentially different from that of other procedural sedative and analgesic agents, especially in terms of pharmacology [6]. The agent simply disconnects the thalamocortical and limbic systems, thus effectively dissociates the central nervous system from outside stimuli resulting in "sensorial isolation". This trance-like cataleptic state eventuates as potent analgesia, sedation, and amnesia while maintaining cardiovascular stability, and preserving spontaneous respirations and protective airway reflexes [7, 8].

In the present study, a vast population of pediatric patients undergone daily surgery for various reasons in whom sedoanalgesia was used was involved. Using a preceding appropriate premedication, whether intraoperative consumption of ketamine would reduce and provide effective intra- and postoperative analgesia followed by an effective local anesthesia with bupivacaine infiltration was assessed.

## Material and methods

All patients administered ketamine for sedoanalgesia were retrospectively evaluated in pediatric surgery clinic of State Hospital of Isparta

**Table 1.** Age and gender distribution

| Age (year) | Girl (n) | Boy (n) | Total (n - %) |
|---|---|---|---|
| Infant (under 1 year) | 18 | 165 | 183 - 6.72 |
| 1 | 18 | 207 | 225 - 8.27 |
| 2 | 10 | 222 | 232 - 8.52 |
| 3 | 14 | 172 | 186 - 6.83 |
| 4 | 4 | 186 | 190 - 6.98 |
| 5 | 7 | 224 | 231 - 8.49 |
| 6 | 17 | 257 | 274 - 10.07 |
| 7 | 5 | 284 | 289 - 10.62 |
| 8 | 11 | 299 | 310 - 11.40 |
| 9 | 6 | 268 | 274 - 10.07 |
| 10 | 8 | 180 | 188 - 6.91 |
| 11 | 7 | 60 | 67 - 2.46 |
| 12 | 4 | 26 | 30 - 1.10 |
| 13 | 6 | 11 | 17 - 0.62 |
| 14 | 3 | 8 | 11 - 0.40 |
| 15 | 2 | 6 | 8 - 0.29 |
| 16 | 1 | 4 | 5 - 0.18 |
| Total | 141 (5.18%) | 2579 (94.81%) | 2720 - 100 |

between 2007 and 2010. Patients were evaluated and selected for sedoanalgesia preoperatively by pediatric surgeons and anesthetists. In pediatric surgery clinic, patients were sent to the operating room by ward nurse after preparation. All data were retrospectively obtained from in the file archive.

Sedoanalgesia was performed to the patients mostly admitted for traditional circumcision, and ones with inguinoscrotal pathologies including groin hernia, hydrocele, undescended testes, and hypospadias and other minor surgical procedures The inclusion/exclusion criteria used in the study according to the guidelines followed by the Green's group were as follows [6].

*Inclusion*

1. Short surgical procedures especially uncomplicated but those requiring immobilization. 2. Intervention considered likely to create excessive emotional disturbance.

*Exclusion*

1. History of airway instability, tracheal surgery or tracheal stenosis. 2. Active pulmonary infection or disease. 3. Fasting not less than four hours. 4. Cardiovascular disease including heart failure or hypertension. 5. Head injury associated with loss of consciousness, altered mental state or emesis. 6. Central nervous system abnormalities or hydrocephalus. 7. Poorly controlled seizure. 8. Thyroid disorder or on thyroid medicines.

Thirty minutes before taken to the operating room, 0.5 mg/kg midazolam was performed to all cases for the purpose of premedication; smaller patients <10 kg via the nasal route, patients >10 kg per os with fruit juice. Intravenous access was achieved in all patients in the operation room with 22 G or 24 G intracath, and then isomix 1/3 was applied at the maintenance rate infusion of 10 mL/kg/h. The patients were monitored by ECG, SPO2 and non-invasive TA. Ketamine 0.5 mg/kg IV was given first, and subsequently 1-2 mg/kg infiltration anesthesia was applied with 0.5% bupivacaine to the surgical region. After waiting five minutes, IV 0.5 mg/kg of ketamine was repeated, and the surgical procedure was initiated. Additional doses requirements and sedation levels of the patients were evaluated with a score of Ramsey Sedation Scale (RSS). During surgical procedures, RSS of patients kept on scale score of 3-4, additional doses of ketamine was performed 0.25 mg/kg IV, if required. Following surgery, patients with RSS were six were taken to the recovery room. Uncomplicated postop patients were followed for 30 minutes, and transferred to the surgical ward. Patients were kept in close observation by ward nurses. In the postop period, patients with pain were given 10 mg/kg IV paresetamol. Patients with no additional problem or complication were discharged on the same day.

## Results

Median age of 2720 patients included in the study was 5.76 ± 2.12 (0-16 years) (**Table 1**). Youngest patient was 42 days old who underwent circumcision. **Table 2** outlines the types of procedures that underwent sedoanalgesia. Circumcision constitutes the major group and the second was inguinal hernia repair (69.3 and 15.7%, respectively). Post procedural vom-

**Table 2.** List of surgical procedure in our study

| Types of Surgical Procedure | n | % | Operative time (minute) | The initial dose of Ketamine (1 mg/kg, IV) | Received repeated doses of Ketamine (0.25 mg/kg) |
|---|---|---|---|---|---|
| Circumcision | 1884 | 69.26 | 16 ± 4.12 | 2 | 97 |
| One sided inguinal hernia repair and circumcision | 198 | 7.27 | 35 ± 12.64 | 2 | 41 |
| One sided inguinal hernia repair | 229 | 8.41 | 20 ± 8.12 | 2 | 19 |
| Unilateral orchidopexy and Circumcision | 58 | 2.13 | 42 ± 9.56 | 2 | 12 |
| Unilateral orchidopexy | 15 | 0.55 | 24 ± 9.93 | 2 | 1 |
| Hydrocelectomy and Circumcision | 69 | 2.68 | 39 ± 8.71 | 2 | 3 |
| Hydrocelectomy | 22 | 3.38 | 22 ± 12.14 | 2 | 3 |
| Bilateral inguinal hernia repair and Circumcision | 25 | 1.28 | 45 ± 17.68 | 2 | 4 |
| Bilateral inguinal hernia repair | 10 | 0.36 | 32 ± 11.74 | 2 | 1 |
| Hypospadias repair | 53 | 1.94 | 44 ± 22.49 | 2 | 24 |
| Bilateral orchidopexy | 12 | 1.10 | 36 ± 13.87 | 2 | 5 |
| Bilateral orchidopexy and Circumcision | 18 | 0.66 | 49 ± 19.28 | 2 | 6 |
| Urethral fistula repair | 9 | 0.33 | 35 ± 17.51 | 2 | 3 |
| Urethral dilatation | 7 | 0.25 | 5 ± 3.02 | 1 | 1 |
| Benign cyst or tumor removal | 65 | 2.38 | 11 ± 7.11 | 2 | 4 |
| Skin laceration suturing | 16 | 0.58 | 7 ± 2.23 | 2 | 1 |
| Esophageal foreign body removal | 9 | 0.33 | 15 ± 12.24 | 2 | 2 |
| Burn wound debridement | 7 | 0.25 | 16 ± 8.71 | 2 | 1 |
| Short lingual frenulum | 13 | 0.47 | 8 ± 2.08 | 1 | - |
| Total | 2720 | 100 | | | |

iting was the most common side-effect. Others were transient oxygen desaturation and generalized seizures (nine patients showed prominent tonic-clonic jerks after ketamine administration). Recovery time could not be determined due to insufficient recorded data. The list of all adverse effects is seen in **Table 3**.

## Discussion

Sedative, analgesic, and dissociative drugs are used in sedoanalgesia to provide analgesia, sedation, anxiolysis, amnesia, and a short duration of motor control during painful or unpleasant diagnostic and therapeutic procedures [9]. Ketamine is widely used particularly in children anesthesia for surgical procedures [10]. The agent is also given commonly for traditional circumcision [11]. It can be used IV, IM, oral, rectal, and nasal in children undergoing surgery [12]. Ketamine has a well-established role in pediatric anesthesia, and is routinely used for induction and maintenance of anesthesia [13]. The state of ketamine's dissociative sedation cannot be easily categorized as either moderate or deep sedation; the agent is considered to have a wide interval of safety [14]. In present study, the level of sedation was administered according to the course of the operation (i.e. moderate in circumcision; deep in hypospadias). The common dosage of Ketamine is 0.5 to 2 mg/kg IV, or 4 to 5 mg/kg IM. The cardiovascular stability has polished it as a popular induction agent in pediatric anesthesia for children with heart disease [15]. Its clinical pharmacology, pharmacokinetics, and especially combination with sedatives were well-studied. Diazepam is especially helpful in reducing the emergence delirium of ketamine [16].

Like other psychoactive agents, ketamine, too, is increasingly abused due to its hallucinogen and euphoric effects [17]. The liquid form can be consumed in drinks, or added to volatile materials. Some extraordinary consequences of ketamine use, as "club drugs" have become popular among teens and young adults in the

**Table 3.** List of adverse events due to sedoanalgesia in our study

| Adverse events | n | % |
|---|---|---|
| Vomiting | 215 | 7.90 |
| Oxygen saturation levels below 90% | 117 | 4.30 |
| Recovery agitation | 75 | 2.75 |
| Bronchospasm | 29 | 1.06 |
| Apnea | 20 | 0.73 |
| Myoclonic jerks just like a generalized seizures | 9 | 0.33 |
| Prolonged recovery period | 3 | 0.11 |
| Respiratory arrest and required intubation | 2 | 0.07 |
| Cardiac arrest | 1 | 0.03 |

drear world of entertainment. The agent can cause delirium, amnesia, depression, and long-term memory and cognitive difficulties, as well. Unhappily due to its dissociative effect, it is reportedly used as a "date-rape drug" [18].

The clinical usage has become more widespread with the increased understanding of its mechanism of action [19]. Salivary gland activation occurs shortly after administration, which is a serious matter for the surgeon during the operation, and easily overcome by an additional 0.02 mg/kg atropine use [20, 21]. To date, no cases of ketamine-induced aspiration have been reported. It would be important, however, to alert parents to the possibility of this common event since the child could possible become nauseous or vomit on the way back home [22]. In the present study, neither during operations nor after procedures in wards or in the follow-ups was aspiration encountered.

The main adverse effect was vomiting reported as approximately 10% of patients [14]. In a study, the incidence of nausea was 12.1% in children aged five years or older and 3.5% in younger ones. Nausea after ketamine administration seems to be associated with increasing age [23]. In our study, only 7.9% patients were observed vomiting. This condition could be explained by the use of low dose of ketamine due to the effects local anesthetic of bupivacaine.

Ketamine can give rise to myoclonic jerks or involuntary movements which may be exaggerated however are self-limited [24]. On the other hand, seizures associated with ketamine have not been reported before. Whether the prominent tonic-clonic jerks encountered in nine patients of the present study represent myoclonic jerks/involuntary movements or a real seizure event was obscure. These patients had previously been healthy without any associated history of epilepsy, and ketamine was given only for traditional circumcision, after which, on follow-ups, they continued their lives without any neurologic deficits. In our cases we have observed the myoclonic jerks may be associated with of ketamine or may be due to the toxicity of bupivacaine.

Recovery agitation is modestly supposed to be associated with decreasing age and the presence of an underlying medical condition. Excluding high IV doses of ketamine (initial dose ≥2.5 mg/kg or total dose ≥5.0 mg/kg) increase the risk of airway and respiratory adverse events, primarily through an increase in apnea. There seems no connection between dosage and airway complications, emesis, or recovery agitation [23, 25]. In our study, 2.75% patients were observed the recovery agitation. This reason for this was associated with about half of cases which is less than 5 years.

The salivation associated with ketamine administration in the concern of maintained laryngeal reflexes can lead to laryngeal spasm when the throat is subjected to mechanical stimuli. In low-dose ketamine pediatric cases, the incidence of laryngeal and bronchial spasm is reported to be very low [26]. Although we have a large patient population consisting of different surgical procedures, bronchospasm was observed in only 1% of cases. This situation can be explained that bronchodilator effect of ketamine beside to reduce secretions of each patients with preoperative routine atropine. In the present study, laryngospasm was not encountered even if some cases had extraction of foreign body from esophagus by clamping under sedoanalgesia.

Herein this study, two cases of respiratory arrest was encountered in those who were circumcised siblings. Both situations developed after ketamine given, and immediately intubated and recovered. Half an hour later, they woke up spontaneously. Follow-ups were trouble-free. They had a third brother, who also underwent circumcision, on the contrary had no complications. One case of circumcision developed

cardiac arrest inevitably. During the procedure at the seventh minute, pulse began to fall rapidly. Mask ventilation was unavailing. Cardiac massage was applied for 15 seconds, and happily the patient's response was elegant. The procedure was completed without any further complications, though he was not intubated, at all. He was discharged with full recovery. A remised follow-up of the patient's pulse-oximetry readings might be accounted on the worsening was supposed.

Ketamine has been reported to possess several new clinically beneficial properties such as reinforcing the opioid analgesia, prevention of opioid-induced acute tolerance and spinal ischemia, anti-inflammatory actions, preventive effects on recall and awareness during general anesthesia, and anti-tumor actions [27]. An intraoperative small dose reduces post anesthetic shivering due to remifentanil administration [28]. Ketamine seems to be safe and effective in rapid treatment for depression and anxiety [29, 30].

Ketamine is a widely used anesthetic in neonates and children due to its rapid onset of action, short duration of action, effective anesthetic and analgesic properties, and safe respiratory and hemodynamic profile. The possibility of hallucinations, increased intracranial pressure, and neuronal death in an immature brain after the administration of repeated high doses of the agent have limited its further use. The agent does not produce neuronal cell damage caused by as trauma, hypoxia, or ischemia, however, favors its continued clinical use, and the need for further research into increasing its potential clinical applications [13]. Deep sedation techniques often results in prolonged recovery times, and have the presumable hazards of suppression of vital airway and breathing reflexes [14]. Non-invasive neuroimaging of cell death after anesthesia in human infants or identifying a behavioral "phenotype" after anesthetic exposure in infancy are supposed to be still premature and be verified [31]. New evidence and perspectives via advanced investigations in humans should be considered [14].

In a study on the respiratory effects of ketamine, ventilatory depression was found to be negligible with a slight increase in the duty cycle (inspiratory time divided by total respiratory cycle time) [32]. However, the utmost was that ketamine increased genioglossus muscle activity while abolishing the coupling between loss of upper airway dilator muscle activity and consciousness. These results might cautiously be extrapolated to humans, given that the airway effects of anesthetics differ between species. The contraction of the large genioglossus muscle elevates the tongue, and pushes it forward, increasing the diameter of the upper airway, thus hampers it collapse [33]. Hypotonia causes posterior displacement to a position where the tongue may drop back, and occlude the pharynx. Therefore, electromyography of the genioglossus has been considered an important indication of upper airway patency [34].

According to the results of a report, raises several questions one of which is whether the respiratory effects of ketamine are dose-dependent [32]. A dose of approximately 1 mg/kg is perhaps the safest in humans; however is it adequate for induction and maintenance of anesthesia under normal conditions?

In pediatric surgical patients in order to ensure adequate comfort volatile anesthetics, regional anesthetic techniques, preemptive and postoperative oral analgesics methods and regimes have been developed [35, 36]. Unfortunately respiratory depression, changes in consciousness, nausea, and vomiting are common side effects of parenteral analgesic opioids. Topical application of local anesthetics does not provide adequate analgesia [37, 38]. In this study we benefited from sedative effects of both midazolam and ketamine, plus both local anesthetic and long term analgesic effects of bupivacaine. Choi et al. used for dorsal penile nerve block is to be circumcised in children local anesthetics lidocaine in the past , but now they have used the bupivacaine that has an important advantage because it provides longer duration of action than the others [39]. In addition we observed that using local anesthesia with bupivacaine has done decreasing the dose of ketamine analgesia next to in the postoperative period provided an effective and long-term analgesia. Weksler et al. [40]. In their study, in children to be circumcised, dorsal penile block and caudal block for postoperative analgesia was compared, in both groups they found a long-lasting effect of postoperative analgesia. However, it was reported that circumcision is performed penile block with 0.25% bupiva-

caine, to just a few children who a need for paracetamol at home after discharge. In some studies were reported that during the application of local anesthesia may be observed in the local hematoma and edema [41], may be occurred systemic toxicity due to systemic absorption of local anesthetics [42]. Also rarely arterial compression [43] or depending on vasoconstrictive effects of local anesthetics can be seen ischemia on the some structures was expressed [40].

In conclusion, our knowledge's regarding the anesthetic management of patients who undergo outpatient surgery sedoanalgesia is suggested as an effective method. Our results recommend, ketamine sedoanalgesia, which has become a rational candidate for limitless clinical usage, in children requiring sedation for a variety of surgical procedures.

## Acknowledgement

We would like to thank Steven M. Green, MD Professor of Emergency Medicine and Pediatrics, Loma Linda University for his contributions.

**Address correspondence to:** Dr. Aybars Ozkan, Dpartment of Pediatric Surgery, School of Medicine, University of Duzce, 81620, Duzce, Turkey. Tel: +90 380 5421387; Fax: +90 380 5421386; Mobile Phone: +90 533 347 6096; E-mail: aybarsozkan@yahoo.com; aybarsozkan@duzce.edu.tr

## References

[1] Munro HM, Malviya S, Lauder GR, Voepel-Lewis T, Tait AR. Pain relief in children following outpatient surgery. J Clin Anesth 1999; 11: 187-91.

[2] Gauntlett I. A comparison between local anaesthetic dorsal nerve block and caudal bupivacaine with ketamine for paediatric circumcision. Paediatr Anaesth 2003 Jan; 13: 38-42.

[3] Wolf AR. Tears at bedtime: a pitfall of extending paediatric day-case surgery without extending analgesia. Br J Anaesth 1999; 82: 319-320.

[4] Achar S, Kundu S. Principles of Office Anesthesia: Part I. Infiltrative Anesthesia. Am Fam Physician 2002 Jul 1; 66: 91-95.

[5] Jobeir A, Galal MO, Bulbul ZR, Solymar L, Darwish A, Schmaltz AA. Use of low-dose ketamine and/or midazolam for pediatric cardiac catheterization. Pediatr Cardiol 2003; 24: 236-43.

[6] Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011; 57: 449-61.

[7] Corssen G, Reves JG, Stanley TH, eds. Intravenous Anesthesia and Analgesia. Philadelphia, PA: Lea & Febiger, 1988, pp: 99-174.

[8] Green SM, Johnson NE. Ketamine sedation for pediatric procedures: Part 2, Review and implications. Ann Emerg Med 1990; 19: 1033-1046.

[9] Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet 2006; 367: 766-80.

[10] Lin C, Durieux ME. Ketamine and kids: an update. Paediatr Anaesth 2005; 15: 91-97.

[11] Ozkan A, Ozorak A, Oruç M. Retrospective Investigation of Complications in Nineteen Hundred Cases of Circumcision. Konuralp Tip Dergisi 2012; 4: 8-12.

[12] Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth 1996; 77: 203-207.

[13] Bhutta AT. Ketamine: a controversial drug for neonates. Semin Perinatol 2007; 31: 303-308.

[14] National Clinical Guideline Centre (UK). Sedation in Children and Young People: Sedation for Diagnostic and Therapeutic Procedures in Children and Young People [Internet]. London: Royal College of Physicians (UK); 2010 Dec. (NICE Clinical Guidelines, No. 112.) Available from: http://www.ncbi.nlm.nih.gov/books/NBK82237/.

[15] Schmitz ML, Ullah S. Right-sided obstructive lesions. In: Andropoulos DB, Stayer SA, Russell IA, eds. Anesthesia for Congenital Heart Disease. United States of America: Futura Blackwell Publishing, 2005; pp: 328-344.

[16] Fontenot J, Wilson RD, Domino EF, Zsigmond EK, Steen SN, Aldrete JA, McDonald JS, Fox GS. Efficacy and safety of low-dose intravenous (mini-drip) ketamine hydrochloride and concurrent intravenous diazepam in the induction and maintenance of balanced anesthesia. Clin Pharm Ther 1982; 31: 225-6.

[17] Jansen KL. A review of the nonmedical use of ketamine: use, users and consequences. J Psychoactive Drugs 2000; 32: 419-33.

[18] http://www.justice.gov/dea/concern/ketamine_factsheet.html.

[19] Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 1989; 36: 186-97.

[20] Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg 1998; 87: 1186-93.

[21] Heinz P, Geelhoed GC, Wee C, Pascoe EM. Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. Emerg Med J 2006; 23: 206-9.
[22] Dolansky G, Shah A, Mosdossy G, Rieder M. What is the evidence for the safety and efficacy of using ketamine in children? Paediatr Child Health 2008; 13: 307-8.
[23] 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, Losek JD; Emergency Department Ketamine Meta-Analysis Study Group. 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: 171-80.
[24] Green SM, Nakamura R, Johnson NE. Ketamine sedation for pediatric procedures: Part 1, A prospective series. Ann Emerg Med 1990; 19: 1024-32.
[25] Green SM, Kuppermann N, Rothrock SG, Hummel CB, Ho M. Predictors of adverse events with intramuscular ketamine sedation in children. Ann Emerg Med 2000; 35: 35-42.
[26] Green SM, Roback MG, Krauss B. Emergency Department Ketamine Meta-Analysis Study Group. Laryngospasm during emergency department ketamine sedation: a case-control study. Pediatr Emerg Care 2010; 26: 798-802.
[27] Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth 2011; 107: 123-6.
[28] Nakasuji M, Nakamura M, Imanaka N, Tanaka M, Nomura M, Suh SH. An intraoperative small dose of ketamine prevents remifentanil-induced postanesthetic shivering. Anesth Analg 2011; 113: 484-7.
[29] Irwin SA, Iglewicz A. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. J Palliat Med 2010; 13: 903-8.
[30] Zarate CA Jr, Brutsche N, Laje G, Luckenbaugh DA, Venkata SL, Ramamoorthy A, Moaddel R, Wainer IW. Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression. Biol Psychiatry 2012; 72: 331-8.
[31] Anand KJ. Anesthetic neurotoxicity in newborns: should we change clinical practice? Anesthesiology 2007; 107: 2-4.
[32] Eikermann M, Grosse-Sundrup M, Zaremba S, Henry ME, Bittner EA, Hoffmann U, Chamberlin NL. Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. Anesthesiology 2012; 116: 35-46.
[33] Oliven A, O'Hearn DJ, Boudewyns A, Odeh M, De Backer W, van de Heyning P, Smith PL, Eisele DW, Allan L, Schneider H, Testerman R, Schwartz AR. Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea. J Appl Physiol 2003; 95: 2023-9.
[34] Canet J, Castillo J. Ketamine: a familiar drug we trust. Anesthesiology 2012; 116: 6-8.
[35] Dahl V, Raeder JC, Drosdal S, Wathne O, Brynildsrud J. Prophylactic oral ibuprofen or ibuprofen-codeine versus placebo for postoperative pain after primary hip arthroplasty. Acta Anaesthesiol Scand 1995; 39: 323-6.
[36] Holthusen H, Eichwede F, Stevens M, Willnow U, Lipfert P. Pre-emptive analgesia: comparison of preoperative with postoperative caudal block on postoperative pain in children. Br J Anaesth 1994; 73: 440-2.
[37] Lander J, Brady-Fryer B, Metcalfe JB, Nazarali S, Muttitt S. Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. JAMA 1997 Dec 24-31; 278: 2157-62.
[38] Chambers FA, Lee J, Smith J, Casey W. Post-circumcision analgesia: comparison of topical analgesia with dorsal nerve block using the midline and lateral approaches. Br J Anaesth 1994 Oct; 73: 437-9.
[39] Choi WY, Irwin MG, Hui TW, Lim HH, Chan KL. EMLA cream versus dorsal penile nerve block for post circumcision analgesia in children. Anesth Analg 2003; 96: 396-9.
[40] Weksler N, Atias I, Klein M, Rosenztsveig V, Ovadia L, Gurman GM. Is penile block better than caudal epidural block for postcircumcision analgesia? J Anesth 2005; 19: 36-9.
[41] Serour F, Reuben S, Ezra S. Circumcision in children with penile block alone. J Urol 1995; 153: 474-476.
[42] Goulding FJ. Penile block for postoperative pain relief in penile surgery. J Urol 1981; 126: 337-338.
[43] Sara CA, Lowry CJ. A complication of circumcision and dorsal nerve block of the penis. Anaesth Intensive Care 1985; 13: 79-85.