Observational Study

Medicine®

OPEN

Flumazenil reduces respiratory complications during anesthesia emergence in children with preoperative upper respiratory tract infections

Ruiqiang Sun, MS[a], Guolin Wang, MD[b,*], Xuesong Gao, MS[a], Shuzhen Wang, MS[a]

Abstract

Despite its benignity, upper respiratory infections (URIs) 1 increase the risk of postoperative respiratory complications during the perioperative and postoperative periods. Flumazenil could improve the symptoms of respiratory obstruction.

To evaluate the effect of flumazenil on the occurrence of respiratory complications during anesthesia emergence of children with preoperative URI.

This was a prospective study of 164 consecutive pediatric patients who underwent strabismus surgery under general anesthesia at the Tianjin Eye Hospital between August 2016 and April 2017. The patients were grouped as: normal airway (N), recent mild URI (I), normal airway and flumazenil (NF), and recent mild URI and flumazenil (group IF) (n = 41/group). An initial dose of flumazenil (0.1 mg) was administrated intravenously to groups IF and NF. The intraoperative and postoperative respiratory complications were recorded by one anesthesiologist unaware of the grouping.

All patients underwent surgery uneventfully. The incidence of postoperative respiratory complications in post-anesthesia care unit (PACU) was higher in group I compared with the other 3 groups (IF: 17%; I: 41%; NF: 5%; N: 10%; $P = .0147$). During the PACU period, significant differences among groups were seen for cough (IF: 15%; I: 20%; NF: 2%; N: 0%; $P = .004$), secretion (IF: 17%; I: 29%; NF: 5%; N: 7%; $P = .007$), low oxygen saturation (IF: 12%; I: 32%; NF: 2%; N: 7%; $P = .001$), and glossocoma (IF: 15%; I: 34%; NF: 10%; N: 32%; $P = .015$).

Respiratory complications during anesthesia emergence were higher in patients with recent preoperative URI compared to patients with healthy airways. Postoperative flumazenil could reduce the incidence of glossocoma.

Abbreviations: ANOVA = analysis of variance, ASA = American Society of Anesthesiologists, BIS = bispectral index, ECG = electrocardiogram, LMA = laryngeal mask airway, LSD = least significant difference, PACU = post-anesthesia care unit, SD = standard deviation, URI = upper respiratory infections.

Keywords: airway complication, flumazenil, general anesthesia, upper respiratory infection

1. Introduction

Upper respiratory infections[1] are a group of diseases sharing common symptoms of nasal congestion, rhinorrhea, cough, sneezing, and sore throat.[2] Generally, URI is self-limited and is of viral origin.[3] About 60% of children show cold symptoms over a month,[4] making URI one of the most common diagnoses made in ambulatory care.[5]

Despite its benignity, URI increases the risk of postoperative respiratory complications during the perioperative and postoperative periods because of the pre-existing inflammation and edema of the upper respiratory tract.[6–10] Specific anesthesia management should be considered for patients with a 2 to 6-week history of URI prior to surgery.[10,11]

Flumazenil is a specific competitive inhibitor of the benzodiazepine receptor, acting through binding to the neurotransmitter gamma-aminobutyric acid (GABA) receptor in the brain.[12] It is primarily used to reduce the residual effects of benzodiazepine including sedation, amnesia, respiratory depression, and muscle relaxation.[13,14] In addition, flumazenil was also reported to act as antagonist of sevoflurane and propofol to shorten anesthesia emergence, and this effect was also considered to be related to competitive binding to the GABA receptor.[15] Midazolam and diazepam are commonly used pre-anesthesia drugs since they can ameliorate nervous emotions in children and facilitate anesthesia induction, but they can also lead to glossocoma and airway constriction[16,17] and subsequent increased airway complications during anesthesia emergence.

Flumazenil has been reported to be able to improve the symptoms of respiratory obstruction caused by glossocoma and airway constriction[18] and to shorten the recovery period after cessation of anesthetic delivery. Therefore, it could help reduce respiratory complications during anesthesia emergence of children with preoperative URI. Therefore, the aim of the present study was to evaluate the effect of flumazenil on the occurrence of respiratory complications during anesthesia emergence of children with preoperative URI.

Editor: Jian Liu.

Competing interests: All authors declare that they have no competing interests.

The authors have no conflicts of interest to disclose.

[a] Cinical College of Ophthalmology, Tianjin Medical University, [b] General Hospital of Tianjin Medical University, Tianjin, China.

[*] Correspondence: Guolin Wang, Department of Anesthesiology, Tianjin Medical University General Hospital, Tianjin 300054,China. (e-mail: wang_guolin@hotmail.com).

Medicine (2018) 97:17(e0516)

Received: 18 September 2017 / Received in final form: 12 March 2018 / Accepted: 28 March 2018

http://dx.doi.org/10.1097/MD.0000000000010516

2. Methods

2.1. Study design and patients

This was a prospective study of 164 pediatric patients who underwent strabismus surgery under general anesthesia at the Tianjin Ophthalmological Hospital between August 2016 and April 2017. The inclusion criteria were: planned for strabismus surgery; grade 1–2 according to the Physical Status Classification system of the American Society of Anesthesiologists[18] ; and parents provided informed consent. The exclusion criteria were: <1 or >10 years of age; height >130 cm; history of gastroesophageal reflux disease or esophageal hiatal hernia; body mass index (BMI) >35 kg/m^2; or uncontrolled severe respiratory infections (according to symptoms of severe cough, high fever, or dyspnea).

The study was approved by the ethics committee of the Tianjin Eye Hospital. Informed consent was obtained from parents of all participants.

2.2. Grouping

The patients were classified into 4 groups: normal airways (group N, n = 41); recent mild URI (group I, n = 41); normal airways and treated with flumazenil (group NF, n = 41); and recent mild URI and treated with flumazenil (group IF, n = 41). The patients in the I group had the lowest frequency in a clinical setting and were consecutively enrolled. Age and gender matched subjects were enrolled in the other groups.

2.3. Anesthesia

Anesthesia was performed by 1 anesthesiologist (attending physician with anesthesia experience of 10 years). Preoperative inquiry included URI within the past 6 weeks.[19] Signs and symptoms were recorded such as running nose, nasal congestion, frequent sneezing, sore throat, hoarseness, cough, temperature ≥38°C, and fatigue. The definition of URI was based on previous studies,[8,11,20] that is, the URI was diagnosed in the presence of at least 2 of the symptoms or signs described above; the parents had recent history or were having URI. The physical examination of the patients was conducted by the anesthesiologist. The severity of URI was evaluated according to the symptoms of cough with sputum, cough during night sleep and interfering sleep quality, body temperature ≥38°C, or dyspnea. The risk factors relevant to respiratory complications were also evaluated such as allergic history (anesthesia drugs, dusts, or odor gases), passive smoking, and asthma history.

The anesthesia management was standardized. The patients received intramuscular injection of midazolam at 0.1 mg/kg (Nhwa Pharmaceutical Co., Ltd., Xuzhou, China) 30 minutes before transfer to the operation room and penehyclidine hydrochloride at 0.01 mg/kg (Chengdu Lisite Pharmaceutical Co., Ltd., Chengdu, China). In the operation room, the patients were inducted by inhalation of 8% sevoflurane (oxygen flow: 6 L/min, without prefilling). The vein channel on the left lower extremity was established when the patients lost consciousness; confirmed by the trapezius squeeze test,[21] followed by placement of a laryngeal mask airway[22] of the appropriate type according to the instructions. The outer surface of the LMA was covered with water-soluble lubricants before insertion and the LMA was fixed well. The anesthesia was performed with a pump providing constant infusion of remifentanil at 0.05 μg/kg/min and was maintained with 2% to 3% sevoflurane (oxygen flow: 2 L/min). The spontaneous respiration of patients was sustained, and manual ventilation was used if necessary to maintain the CO_2 below 55 mm Hg at the end of expiration and SPO_2 above 96%. The depth of anesthesia was routinely monitored by the bispectral index[23] from the beginning of anesthesia to emergence, including during transfer to post-anesthesia care unit (PACU). The anesthesia was terminated before the operation completed, that is, when the conjunctiva was sutured. LMA was removed immediately after operation, the air within the cuff of the LMA was not released before removal and vacuum suction of the airways was not performed. The patients were transferred to the PACU upon recovery of spontaneous respiration after LMA removal (tidal volume ≥6 mL/kg, breathing frequency ≥12 bpm). Oxygen saturation was monitored during transfer and mask oxygen was given, the transfer took less than 3 minutes. Close monitoring was conducted once the patients were transferred to the PACU, including pulse, oxygen saturation, nasal end expiratory CO_2, blood pressure, heart rate, and electrocardiogram (ECG). A dose of flumazenil 0.1 mg was administrated intravenously to patients from groups IF and NF (Fig. 1).

The respiratory complications were recorded by an anesthesiologist blinded to grouping, including primary events such as cough, airway excessive secretions, bronchial spasm, laryngeal spasm, and oxygen saturation decreased by >10% compared to before anesthesia induction; and the secondary events such as all emergency measures such as intravenous injection of muscle relaxants, deepening the anesthesia, pressurized oxygen supply, and placing oropharyngeal airway and laryngeal mask. Even a single episode of cough would be recorded. The incidence of complications was calculated by the percentage of patients with complication among the total number of patients. The complications were recorded during the intraoperative and PACU periods. The duration of PACU stay was recorded, starting upon entering until a Steward score of 6 was achieved.

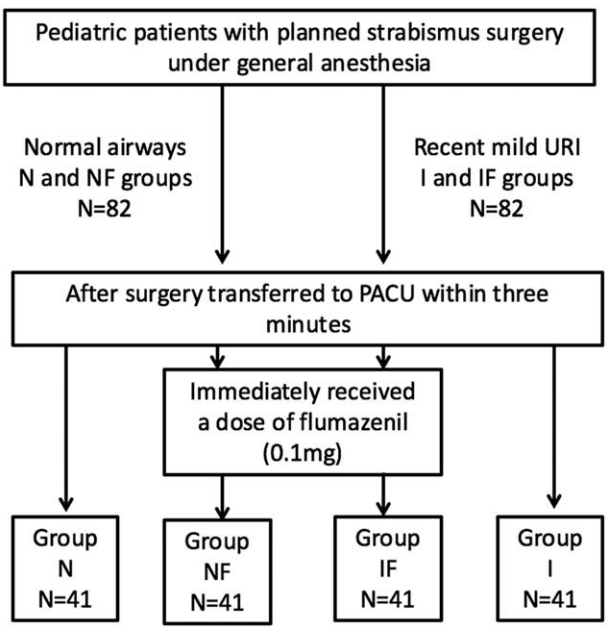

Figure 1. Flow chart showing the patient grouping and administration of flumazenil.

Table 1

Characteristics of the patients.

	Upper respiratory infection		Healthy airways		
	IF (n=41)	I (n=41)	NF (n=41)	N (n=41)	P
Age	5.2±2.0	5.2±1.7	5.8±1.6	5.5±1.1	0.343
Height, cm	110±13	111±10	114.6±9	115±10	0.080
Weight, kg	19.1±4.2	19.3±3.8	20.3±3.9	19.2±2.0	0.426
ASA (1/2)	40/1	41/0	39/2	40/1	0.562
Passive smoking, n (%)	19 (46.3)	16 (39.0)	21 (51.2)	18 (43.9)	0.734
History of asthma	0	0	0	0	
History of allergy	0	0	0	0	
Operation time, minutes	19.8±6.2	20.4±5.4	18.6±5.8	19.2±6.9	0.663
PACU stay period, minutes	14.2±3.8	16.1±4.2	13.6±4.5	14.8±5.0	0.396

ASA=American Society of Anesthesiologists, PACU=post-anesthesia care unit.

2.4. Statistical analysis

Mean±standard deviation (SD) was used to describe the continuous data that showed normal distribution according to the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) and least significant difference (LSD) post-hoc test were used for multigroup analysis for continuous data. Categorical data were presented as frequencies and analyzed using the chi-square test or Fisher's exact test, as appropriate. Two-sided *P*-values <.05 were considered statistically significant.

3. Results

3.1. Characteristics of the patients

There was no significant difference among the 4 groups regarding age, height, weight, ASA score, history of force smoking, history of asthma, and history of allergy (all $P>.05$) (Table 1). All surgeries were completed successfully. Operation time ($P=.663$) and PACU stay ($P=.396$) were similar among the 4 groups.

3.2. Intraoperative and postoperative respiratory complications

There was no significant difference among 4 groups regarding to the incidence of intraoperative respiratory complications (IF: 10%; I: 12%; NF: 5%; N: 7%; $P>.05$). The PACU complications (IF: 17%; I: 41%; NF: 5%; N: 10%; $P=.0147$) and the incidence of total complications (IF: 17%; I: 41%; NF: 5%; N: 10%; $P=.0147$) in group I were higher compared with the other 3 groups (Table 2).

There were no significant differences regarding intraoperative respiratory infection, cough, secretions, low oxygen saturation, and laryngeal spasm among the 4 groups (all $P>.05$). During the PACU period, the incidences of cough (IF: 15%; I: 20%; NF: 2%; N: 0%; $P=.004$), secretion (IF: 17%; I: 29%; NF: 5%; N: 7%; $P=.007$), low oxygen saturation (IF: 12%; I: 32%; NF: 2%; N: 7%; $P=.001$), and glossocoma (IF: 15%; I: 34%; NF: 10%; N: 32%; $P=.015$) were higher in groups I and IF than that in groups N and NF (all $P<0.05$); the incidences of glossocoma and low oxygen saturation in group IF were lower than in group I (all

Table 2

Classification of perioperative respiratory complications.

	Upper respiratory infection		Healthy airways	
	IF (n=41)	I (n=41)	NF (n=41)	N (n=41)
Intraoperative				
Cough	4 (10)	3 (7)	0	1 (2)
Secretion	3 (7)	5 (12)	2 (5)	1 (2)
Low oxygen saturation	4 (10)	4 (10)	0	0
Laryngeal spasm	4 (10)	3 (7)	0	0
Total intraoperative	4 (10)	5 (12)	2 (5)	3 (7)
PACU				
Cough	6 (15)*	8 (20)*	1 (2)	0
Secretion	7 (17)*	12 (29)*	2 (5)	3 (7)
Low oxygen saturation	5 (12)#	13 (32)*	1 (2)	3 (7)
Laryngeal spasm	5 (12)	3 (7)	1 (2)	1 (2)
Glossocoma	6 (15)†	14 (34)*	4 (10)‡	13 (32)
Total PACU	7 (17)	17 (41)*	2 (5)	4 (10)
Total complications	7 (17)	17 (41)*	2 (5)	4 (10)

NF=normal airway and flumazenil, PACU=post-anesthesia care unit.

Note: Total number indicates the number of subjects that experienced complications.

* $P<.05$ vs groups N and NF.

† $P<.05$ vs group I.

‡ $P<.05$ vs group N.

$P < .05$); and the incidence of glossocoma in group NF was lower than that in group N (Table 2).

4. Discussion

Despite its benignity, URI increase the risk of postoperative respiratory complications during the perioperative and postoperative periods. Flumazenil could improve the symptoms of respiratory obstruction. The aim of the present study was to evaluate the effect of flumazenil on the occurrence of respiratory complications during anesthesia emergence of children with preoperative URI. The results suggest that respiratory complications during anesthesia emergence were higher in patients with recent preoperative URI compared to patients with healthy airways. Postoperative flumazenil reduced the incidence of glossocoma in patients with URI.

The anatomic features of the upper respiratory tract in children make the airway more susceptible to anesthesia and secretions leading to complication and ventilation obstruction.[22] For elective surgery, the operation shall be postponed if the patient has severe URI, though short and minor operations could be conducted for those with recent but mild URI, the occurrence of respiratory complications are significantly increased.[10,11] In the present study, children with URI had a higher incidence of respiratory complications during anesthesia emergence compared with patients without URI, as supported by previous studies.[6–10]

Flumazenil is a benzodiazepine receptor antagonist binding to GABA receptors in brain tissue, it reverses the residual effects of benzodiazepine[15] and significantly shortens anesthesia emergence, with a high safety profile and seldom cases of eliciting epileptic brain waves.[23] Benzodiazepine is widely used as a preanesthesia drug, though its effect on anesthesia emergence remains controversial. Residual benzodiazepine could lead to central respiratory depression, relaxation of associated respiratory muscles, and collapse of the upper respiratory tract, resulting in airway obstruction and hypoventilation.[24] In the present study, the incidence of respiratory complications during anesthesia emergence in children was observed in order to evaluate the effect of flumazenil on reducing respiratory complications in the patients with recent URI.

In the present study, the patients were pretreated with anticholinergic drugs (penehyclidine hydrochloride and benzodiazepine) and diazepam and were induced with sevoflurane inhalation. The anesthesia was maintained using sevoflurane inhalation and infusion of remifentanil. Though flumazenil is a specific antagonist of benzodiazepine, it has also been reported to counteract the sedative effects of halothane, sevoflurane, and propofol, which might be associated with the GABA receptor.[24,25] The GABA type A (GABA-A) receptor is the major inhibitory ion channel in the brain and is considered to be important for the general mechanism of action of benzodiazepine anesthesia.[25] Flumazenil could counteract the effect of preoperative diazepam and intraoperative sevoflurane. In the present study, the incidence of respiratory complications was significantly higher during anesthesia emergence in patients with recent URI, compared with those with healthy airways, though there was no significant difference regarding the intraoperative complications. The complications during PACU stay were significantly higher in group I than in group N (cough, low oxygen saturation, secretion, and glossocoma), and flumazenil could significantly reduce this difference, since the incidence of complications was significantly lower in group IF compared with group I (low oxygen saturation and glossocoma). These results are supported by Oshima et al,[18] who showed that flumazenil could reverse the nasal airway contraction caused by midazolam in adults, and the incidences of asphyxia and snoring during postoperative recovery period were significantly reduced. Dhonneur et al[17] showed through electromyogram that the relaxation of posterior genioglossus and diaphragm could be induced by midazolam, interfering with ventilation, and that flumazenil could counteract these effects of midazolam. However, it is worth noting that flumazenil cannot antagonize obstruction of the upper respiratory tract and respiratory depression caused by opioids and muscle relaxants. Other commonly used narcotic antagonists include the opioid antagonist naloxone and neostigmine (a muscle relaxant antagonist),[26] which were not used in this study because remifentanil is a short-acting opioid analgesic and theoretically does not need antagonism. In this study, the patients did not receive muscle relaxants. The occurrence of glossosoma was caused by benzodiazepines and the inhalation of anesthetic drugs. Therefore, flumazenil was the most suitable antagonist for the study subjects.

The major safety concern of flumazenil in children is epileptic brain waves induced by flumazenil. A cohort study by Kreshak et al[27] indicated that there was no flumazenil-associated epileptic seizure in 83 patients who were administrated flumazenil to treat benzodiazepine poisoning. Similarly, during anesthesia monitoring of BIS no epileptic brain waves were observed in the present study.

Pediatric strabismus surgery is a minor and short operation, with less operative stimuli and no need for tracheal intubation general anesthesia, and LMA is widely used for this surgery. Therefore, there was no serious concern of postoperative pulmonary infection for patients with mild URI.[28] Since the airway reactivity of children is high, and the complications such as cough and laryngeal spasm were commonly found during anesthesia emergence,[29] laryngeal mask removal under deep anesthesia could reduce the irritation to the airway, but without effect on the subsequent upper airway obstruction and hypoventilation. Flumazenil then could counteract the residual effects of anesthesia drugs to help patients go through the emergence period smoothly and with reduced respiratory complication after anesthetic withdrawal.

The present study has some limitations. The observational nature of the study prevented in determining cause-to-effect relationships. The sample size was small and from a single center. We decided to use 6 weeks as the cut-off point for a history of URI for the patient grouping, which meant that some of the patients in the URI groups may have been free of URI symptoms. However, we were concerned that a shorter cut-off would mean that some patients with residual URI symptoms were considered to be free of URI. We also did not perform any tests for influenza A or B to identify these viral infections within the patients. Additional studies are necessary to confirm these results.

In conclusion, respiratory complications during anesthesia emergence were higher in patients with recent preoperative URI compared to patients with healthy airways. Postoperative flumazenil reduced the incidence of glossocoma in these patients.

Author contributions

Conceptualization: Ruiqiang Sun.
Data curation: Ruiqiang Sun.
Formal analysis: Ruiqiang Sun.
Investigation: Xuesong Gao.

Methodology: Ruiqiang Sun, Guoling Wang.
Project administration: Guoling Wang.
Resources: Ruiqiang Sun.
Software: Ruiqiang Sun.
Supervision: Guoling Wang, Shuzhen Wang.
Validation: Xuesong Gao.
Visualization: Shuzhen Wang.
Writing – original draft: Ruiqiang Sun.
Writing – review & editing: Ruiqiang Sun, Guoling Wang.

References

[1] Collombat P, Xu X, Ravassard P, et al. The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells. Cell 2009;138:449–62.
[2] Heikkinen T, Jarvinen A. The common cold. Lancet 2003;361:51–9.
[3] Fashner J, Ericson K, Werner S. Treatment of the common cold in children and adults. Am Fam Physician 2012;86:153–9.
[4] Kvaerner KJ, Nafstad P, Jaakkola JJ. Upper respiratory morbidity in preschool children: a cross-sectional study. Arch Otolaryngol Head Neck Surg 2000;126:1201–6.
[5] Hsiao CJ, Cherry DK, Beatty PC, et al. National ambulatory medical care survey: 2007 summary. Natl Health Stat Report 2010;1–32.
[6] Cohen MM, Cameron CB. Should you cancel the operation when a child has an upper respiratory tract infection? Anesth Analg 1991;72:282–8.
[7] Rolf N, Cote CJ. Frequency and severity of desaturation events during general anesthesia in children with and without upper respiratory infections. J Clin Anesth 1992;4:200–3.
[8] Tait AR, Malviya S, Voepel-Lewis T, et al. Risk factors for perioperative adverse respiratory events in children with upper respiratory tract infections. Anesthesiology 2001;95:299–306.
[9] Malviya S, Voepel-Lewis T, Siewert M, et al. Risk factors for adverse postoperative outcomes in children presenting for cardiac surgery with upper respiratory tract infections. Anesthesiology 2003;98:628–32.
[10] von Ungern-Sternberg BS, Boda K, Chambers NA, et al. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. Lancet 2010;376:773–83.
[11] Tait AR, Malviya S. Anesthesia for the child with an upper respiratory tract infection: still a dilemma? Anesth Analg 2005;100:59–65.
[12] Wiebking C, Duncan NW, Qin P, et al. External awareness and GABA—a multimodal imaging study combining fMRI and [18F]flumazenil-PET. Hum Brain Mapp 2014;35:173–84.
[13] Rinehart JB, Baker B, Raphael D. Postoperative global amnesia reversed with flumazenil. Neurologist 2012;18:216–8.
[14] Veiraiah A, Dyas J, Cooper G, et al. Flumazenil use in benzodiazepine overdose in the UK: a retrospective survey of NPIS data. Emerg Med J 2012;29:565–9.
[15] Araki H, Fujiwara Y, Shimada Y. Effect of flumazenil on recovery from sevoflurane anesthesia in children premedicated with oral midazolam before undergoing herniorrhaphy with or without caudal analgesia. J Anesth 2005;19:204–7.
[16] Yoshimura H, Kai T, Nishimura J, et al. Effects of midazolam on intracellular Ca^{2+} and tension in airway smooth muscles. Anesthesiology 1995;83:1009–20.
[17] Dhonneur G, Combes X, Leroux B, et al. Postoperative obstructive apnea. Anesth Analg 1999;89:762–7.
[18] Oshima T, Masaki Y, Toyooka H. Flumazenil antagonizes midazolam-induced airway narrowing during nasal breathing in humans. Brit J Anaesth 1999;82:698–702.
[19] Schebesta K, Guloglu E, Chiari A, et al. Topical lidocaine reduces the risk of perioperative airway complications in children with upper respiratory tract infections. Can J Anaesth 2010;57:745–50.
[20] Tait AR, Knight PR. Intraoperative respiratory complications in patients with upper respiratory tract infections. Can J Anaesth 1987;34: 300–3.
[21] Chang CH, Shim YH, Shin YS, et al. Optimal conditions for Laryngeal Mask Airway insertion in children can be determined by the trapezius squeezing test. J Clin Anesth 2008;20:99–102.
[22] Sahin-Yilmaz A, Naclerio RM. Anatomy and physiology of the upper airway. Proc Am Thorac Soc 2011;8:31–9.
[23] Drobish JK, Kelz MB, DiPuppo PM, et al. Emergence delirium with transient associative agnosia and expressive aphasia reversed by flumazenil in a pediatric patient. A A Case Rep 2015;4:148–50.
[24] Safavynia SA, Keating G, Speigel I, et al. Effects of gamma-aminobutyric acid type a receptor modulation by flumazenil on emergence from general anesthesia. Anesthesiology 2016;125:147–58.
[25] Liang P, Zhou C, Li KY, et al. Effect of flumazenil on sevoflurane requirements for minimum alveolar anesthetic concentration-awake and recovery status. Int J Clin Exp Med 2014;7:673–9.
[26] Krauss BS, Krauss BA, Green SM. Procedural sedation and analgesia in children. N Engl J Med 2014;371:91.
[27] Kreshak AA, Tomaszewski CA, Clark RF, et al. Flumazenil administration in poisoned pediatric patients. Pediatr Emerg Care 2012;28: 448–50.
[28] Gharaei B, Aghamohammadi H, Jafari A, et al. Use of laryngeal mask airway in children with upper respiratory tract infection, compared with face mask: randomized, single blind, clinical trial. Acta Anaesthesiol Taiwan 2011;49:136–40.
[29] Splinter WM, Reid CW. Removal of the laryngeal mask airway in children: deep anesthesia versus awake. J Clin Anesth 1997;9:4–7.