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

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Abstract
Despite its benignity, upper respiratory infections (URIs) 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%; \( P = .015 \)), 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 are a group of diseases sharing common symptoms of nasal congestion, rhinorrhea, cough, sneezing, and sore throat. Generally, URI is self-limited and is of viral origin. About 60% of children show cold symptoms over a month, making URI one of the most common diagnoses made in ambulatory care.

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. Specific anesthesia management should be considered for patients with a 2 to 6-week history of URI prior to surgery. Flumazenil is a specific competitive inhibitor of the benzodiazepine receptor, acting through binding to the neurotransmitter gamma-aminobutyric acid (GABA) receptor in the brain. It is primarily used to reduce the residual effects of benzodiazepine including sedation, amnesia, respiratory depression, and muscle relaxation. 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. 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 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 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.
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/m²; 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 pethidine 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 CO₂ below 55 mm Hg at the end of expiration and SPO₂ 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 CO₂, 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.

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Figure 1. Flow chart showing the patient grouping and administration of flumazenil.
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* < .05); the incidences of glossocoma and low oxygen saturation in group IF were lower than in group I (all *P* < .05).

### 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 ± 4.9 | 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.

### Table 2

Classification of perioperative respiratory complications.

|                      | Upper respiratory infection | Healthy airways |
|----------------------|----------------------------|-----------------|
|                      | IF (n=41)                  | I (n=41)        | NF (n=41) | N (n=41) | *P*  |
| Intraoperative       |                            |                |           |           |      |
| Cough                | 4 (10)                     | 3 (7)          | 0         | 1 (0)    |
| Secretion           | 3 (7)                      | 5 (12)         | 2 (5)     | 1 (0)    |
| 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 (0)     | 0        |
| Secretion           | 7 (17)*                    | 12 (29)*       | 2 (5)     | 3 (7)    |
| Low oxygen saturation | 5 (12)*                  | 13 (32)*       | 1 (0)     | 3 (7)    |
| Laryngeal spasm     | 5 (12)                     | 3 (7)          | 1 (0)     | 1 (0)    |
| 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. 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. 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.

Flumazenil is a benzodiazepine receptor antagonist binding to GABA receptors in brain tissue, it reverses the residual effects of benzodiazepine and significantly shortens emergence, with a high safety profile and seldom cases of eliciting epileptic brain waves. 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.

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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.
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