Original Article

# Risk factors for chemotherapy-induced vomiting after general anesthesia in children with retinoblastoma: a retrospective study

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**Background:** The chemotherapy-induced vomiting (CIV) severely affects the daily function, nutritional status, treatment compliance, therapeutic efficacy, curability, and the quality of life of patients. The aim of this study was to find the risk factors for CIV after general anesthesia in patients with retinoblastoma (RB).

**Methods:** A retrospective review of the hospital records of children with RB, who underwent chemotherapy between January 2017 and December 2019, was conducted at our hospital.

**Results:** Data of a total of 803 children with RB were reviewed. The incidence of CIV in children with RB was 19.30%. Univariate analysis showed statistically significant differences in age, height, weight, chemotherapy regimen, anesthesia dose, duration of surgery and general anesthesia, platelet count, platelet distribution width, lymphocytes, and indirect bilirubin between patients with and without vomiting (P<0.05). Multivariate logistic regression analysis showed that the main predictors of CIV in children with RB included older age [odds ratio (OR), 1.32; 95% confidence interval (CI): 1.11–1.56; P<0.01], low platelet count (OR, 0.997; 95% CI: 0.995–0.999; P<0.05), and chemotherapy regimen (intravenous chemotherapy versus intra-arterial chemotherapy; OR, 0.47; 95% CI: 0.29–0.76; P<0.01).

**Conclusions:** This study revealed age, chemotherapy regimen, and platelet count as risk factors of CIV after general anesthesia in children with RB. Younger age and higher platelet count were protective factors for CIV. Compared with intravenous chemotherapy, the incidence of CIV was lower than that of intra-arterial chemotherapy. Although these factors cannot be modified, they can predict whether a patient may experience vomiting, assisting medical staff to formulate measures and intervenes in advance.

**Keywords:** Retinoblastoma (RB); chemotherapy-induced vomiting (CIV); general anesthesia; multivariate analysis; risk factors

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## Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in children (1). In China, there are approximately 1,100 new cases of RB annually (2). At present, the most widely used treatment methods for RB include ocular enucleation, chemotherapy, radiotherapy, cryotherapy, laser therapy, etc. (3). Although there are a large number of treatment methods for RB, the basic methods adopted by the global RB centers mainly involve intravenous chemotherapy (IVC) and intra-arterial chemotherapy (IAC) (4). Chemotherapy has greatly improved the ocular survival rate, eye protection rate, and recovery rate in children with RB. The majority of children with RB need to undergo fundus examination under general anesthesia before chemotherapy to determine a robust treatment plan. In this specific population, ophthalmologists have paid more attention to the therapeutic effects of chemotherapy on ocular tumors, while gastrointestinal complications, such as chemotherapy-induced nausea and vomiting (CINV) or postoperative nausea and vomiting (PONV) have been scarcely studied. Owing to the necessity of assessment and management of CINV or PONV, they currently do not belong to the routine diagnostic and therapeutic schemes in ophthalmology. However, these complications remain the main concern in ophthalmology (1). CINV or PONV could severely affect the daily function, nutritional status, treatment compliance, therapeutic efficacy, curability, and the quality of life of patients (5-7). In recent years, treatment methods for RB have paid additional attention to patients' quality of life during treatment.

CINV is one of the most common adverse events related to chemotherapy in pediatric patients (8). In the absence of preventive drugs, moderately emetogenic chemotherapy (MEC) could cause CINV in 30–90% of cases, while the incidence of CINV with the low emetogenic chemotherapy was reported in the range of 10–30% (9). Patients-associated factors have significantly influenced the risk of CINV, such as history of nausea/vomiting, female gender, younger age, and history of morning sickness (10). Due to the differences in chemotherapy doses and regimens between children and adults, the risk factors of CINV in children may also be different from adults (11). The 2021 clinical practice guideline is strongly recommended to optimize acute and delayed CINV control to prevent anticipatory CINV (12). In the first 24 hours, the complete control rate of highly emetic chemotherapy (HEC) in pediatric patients was 37% and that of MEC in such patients was 24% (5). Although other studies have reported a higher rate of complete control of about 50% (13), the complete control rate of pediatric CINV has still remained low and patients have not received optimal treatment (5). Thus, identification of risk factors of CINV can further improve the control of CINV.

PONV is a frequent complication in pediatric patients undergoing general anesthesia. To date, several studies have identified PONV-associated risk factors. Rüsch *et al.* (14) found that female gender, history of PONV, motion sickness, intraoperative and postoperative administration of opioids, use of inhaled anesthetics and nitrous oxide, and anesthesia time were the relevant risk factors of PONV. Dupuis *et al.* (15) demonstrated that younger age, administration of antiemetic prophylaxis, shorter acute-phase duration, and antiemetic regimen were associated with complete control of chemotherapy-induced vomiting (CIV) in pediatric patients receiving MEC or HEC. Gan *et al.* (16) described specific risk factors for postoperative vomiting (POV) in children (age >3 years old, eye surgeries, duration of surgery >30 min, family history, etc.). An exploratory study (17) found that the number of platelets was associated with the occurrence of PONV. The platelet count, mean platelet volume and their ratio may be used to predict POV in children (18). Karaca *et al.* (19) reported that platelet-to-lymphocyte ratio (PLR) or neutrophil-to-lymphocyte ratio (NLR) could be used to predict inflammatory diseases. They pointed out that preoperative NLR and PLR could be considered in antiemetic regimens to prevent PONV.

Although several studies have concentrated on the risk factors of CINV or POV, there are few reports on the risk factors of CIV after general anesthesia in infants, especially in children with RB. Oncologists have clarified the vomiting-associated risk factors and the application of these factors to identify patients with high-risk of vomiting before chemotherapy. Early targeted intervention can improve patients' quality of life and treatment compliance, so as to improve the overall efficacy of treatment (10). After analyzing the risk factors of a particular group of patients, effective and accessible interventions based on specific conditions of such patients could be formulated. We use VEC regimen (vincristine, etoposide, and carboplatin) in IVC group, and melphalan, topotecan, carboplatin in IAC group. The mean duration of chemotherapy block was 1–2 days. Among the drugs used in chemotherapy for RB patients, carboplatin has a moderate risk of vomiting (0–90%), etoposide and topotecan have a low risk of vomiting (10–30%), and vincristine and melphalan have

a slight risk of vomiting (<10%) (20). All children used a two-drug combination of ondansetron and dexamethasone to prevent vomiting caused by chemotherapy after general anesthesia. The present study only concentrated on CIV, rather than chemotherapy-induced nausea, and it was attempted to evaluate the risk factors of CIV in RB patients, and to provide a robust reference for the prevention of CIV in such patients. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tp-21-245).

## Methods

### *Study design*

Data of children with RB who were treated in the Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai, China) between January 2017 and December 2019 were retrospectively analyzed. For children with repeated hospitalization, each hospitalization was recorded as an event. The inclusion criteria were as follows: all children with RB who aged <5 years old, underwent fundus examination under general anesthesia, and only received chemotherapy block. After waking up in the recovery room for 2 h, patients returned to the ward and underwent chemotherapy. Patients with metastatic brain tumors or those who also suffered from other diseases that could cause vomiting were excluded. The primary study endpoint was the times of vomiting in children with RB under the dual effects of chemotherapy and general anesthesia. We reviewed a large number of previous studies on predictive variables related to vomiting, combined with clinical experience and onset age of RB. Finally, the predictive variables of vomiting included in this study were age, gender, height, weight, laterality at the time of diagnosis, ocular enucleation, chemotherapy regimen, vomiting, auxiliary medicine, dexamethasone, anesthetics (e.g., midazolam, rocuronium, ketamine, sevoflurane), fundal examination time, duration of anesthesia, platelet count, and platelet distribution width.

We designed an electronic questionnaire in order to extract the variables listed above. The scope of this study was limited to the emergence of vomiting in the acute phase (i.e., 24-h period following administration of chemotherapy) and did not include anticipatory, breakthrough or delayed phase, or radiation-related vomiting. In the present study, vomiting was defined as retching and expulsion of the stomach's contents through the mouth. Vomiting events with an interval of more than 1 min were regarded as two independent vomiting events. Our nursing team paid attention to the vomiting caused by chemotherapy. It was a practice standard for nurses to record the listed information on a standardized form, which was stored in the medical record.

### *Statistical analysis*

Descriptive statistics were used to describe patients' general demographic and clinical characteristics. If continuous data obey a normal distribution, they were expressed as mean±standard deviation; otherwise, they were presented as median (minimum, maximum). The classification data were described in form of the number of cases (percentage). The comparison between two independent groups was performed using the independent-samples *t*-test or Chi-square test. The times of vomiting was taken as a dependent variable, and each effective factor was regarded as an independent variable. Univariate analysis was conducted first, then multivariate logistic regression analysis was undertaken for finding significant variables ($P<0.05$) and borderline significant variables. The test criteria ($\alpha \leq 0.05$ as the inclusion threshold and $\alpha \geq 0.10$ as the exclusion threshold) were used to construct the regression equation. A stepwise logistic regression was used to generate a final model. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were reported. All data were statistically analyzed using SPSS 25.0 software (IBM, Armonk, NY, USA). A two-sided $P<0.05$ was considered statistically significant.

### *Ethical statement*

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the Institutional Review Board of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (approval number SH9H-2019-T291-3). Due to the retrospective nature of this study, informed consent was waived.

## Results

### *Patients' demographic and clinical characteristics*

The mean values of age, weight, height, and platelet count

 

**Table 1** Patients' demographic and clinical characteristics (N=803)

| Characteristic | Mean ± SD/n (%) |
|---|---|
| Age (years), mean ± SD/median (minimum, maximum) | 2.35±2.02/2.39 (0.09, 4.96) |
| Weight (kg) | 13.44±8.41 |
| Height (length) (cm) | 88.70±16.94 |
| Midazolam dose (mg) | 0.87±0.46 |
| Rocuronium (mg) | 10.28±5.83 |
| Dexamethasone (mg) | 2.29±0.66 |
| Ketamine (mg) | 58.75±41.86 |
| Sevoflurane inhalation time (min) | 52.01±57.29 |
| Fundal exam time (min) | 47.56±53.99 |
| Duration of anesthesia (min) | 58.39±57.40 |
| Platelet count ($10^9$/L) | 276.31±89.40 |
| Platelet volume distribution width (fL) | 11.34±4.51 |
| Lymphocytes ($10^9$/L) | 3.50±1.97 |
| Indirect bilirubin (μmol/L) | 5.56±2.67 |
| Gender | |
| Male | 391 (48.7) |
| Female | 412 (51.3) |
| Laterality at diagnosis | |
| Unilateral | 625 (77.8) |
| Bilateral | 178 (22.2) |
| Ocular enucleation | |
| Yes | 56 (7.0) |
| No | 747 (93.0) |
| Treatment | |
| IVC | 537 (66.9) |
| IAC | 266 (33.2) |
| CIV | |
| Vomiting | 155 (19.3) |
| No-vomiting | 648 (80.7) |
| Manage of CIV | |
| Ondansetron | 47 (30.3) |
| Metoclopramide | 96 (61.9) |
| No-antiemetics | 12 (7.7) |

IAC, intra-arterial chemotherapy; IVC, intravenous chemotherapy; CIV, chemotherapy-induced vomiting.

of the children in this survey were 2.35 years old, 13.44 kg, 88.70 cm, and 276.31×$10^9$/L, respectively. The male:female ratio was within 1:1. Of the 803 patients, RB patients were mainly unilateral (77.8%), and ocular enucleation rate was low (7%). VEC regimen was dominantly used in our center, and arterial IAC regimen account for only 33.2%. Although we followed the guidelines and all children received a combination of 5-HT3 receptor antagonist and dexamethasone to prevent vomiting, the incidence of CIV was 19.3% (155/803), and auxiliary medicine was administered to 92.3% (143/155) of patients who suffered from vomiting (*Table 1*).

### *The effects of auxiliary antiemetics*

The results of Chi-square test showed that different interventions have different relief effects on vomiting (P=0.026). Pair-wise comparison demonstrated that ondansetron has a superior overall relief compared with metoclopramide (P=0.007), indicating no significant difference among the observation, ondansetron, and metoclopramide groups (*Table 2*).

### *Single factor analysis of vomiting in children with RB*

Univariate analysis showed significant differences in age, height, weight, treatment, anesthetic drug dose, duration of surgery and anesthesia, platelet count, platelet distribution width, indirect bilirubin, and lymphocytes between the vomiting and non-vomiting groups (P<0.05), while gender, presence of ocular enucleation, diseased eye and manage of CIV did not exhibit statistically significant differences (P>0.05, *Table 3*).

### *Multivariate logistic regression analysis of vomiting in children with RB*

Analyses were adjusted for age, gender, laterality at diagnosis, presence of ocular enucleation, and auxiliary medicine. Multivariate logistic regression analysis was conducted on times of vomiting as a dependent variable, and the results revealed that age, chemotherapy regimen, and platelet count were independent factors influencing vomiting (*Table 4*).

## Discussion

Chemotherapy is still one of the most important treatment

**Table 2** The effects of auxiliary antiemetics

| Group | Total | Slightly relieved, n (%) | Complete relieved, n (%) | $\chi^2$ value | P value |
|---|---|---|---|---|---|
| Ondansetron | 47 | 11 (23.4) | 36 (76.6) | 7.31 | 0.026 |
| Metoclopramide | 96 | 45 (46.9) | 51 (53.1) | | |
| No-antiemetics | 12 | 5 (41.7) | 7 (58.3) | | |

CIV, chemotherapy-induced vomiting; RB, retinoblastoma.

**Table 3** Single factor analysis of vomiting in children with RB (N=803)

| Risk factor | Non-CIV (n=648) | CIV (n=155) | $t/\chi^2$ | P |
|---|---|---|---|---|
| Age (years) | 2.65±1.79 | 3.14±1.64 | 0.08 | <0.001 |
| Weight (kg) | 14.05±6.22 | 15.10±4.99 | 0.24 | 0.043 |
| Height (Length) (cm) | 90.83±14.84 | 95.78±14.24 | 1.35 | <0.001 |
| Midazolam dose (mg) | 0.85±0.47 | 0.97±0.46 | 2.08 | 0.007 |
| Rocuronium (mg) | 9.89±5.63 | 11.33±6.58 | 1.21 | 0.030 |
| Dexamethasone (mg) | 2.26±0.63 | 2.42±0.82 | 2.12 | 0.007 |
| Ketamine (mg) | 52.06±41.95 | 96.67±5.77 | 48.08 | <0.001 |
| Sevoflurane inhalation time (min) | 48.86±56.52 | 70.20±58.54 | 9.81 | <0.001 |
| Fundal exam time (min) | 44.20±52.73 | 66.93±57.31 | 14.20 | <0.001 |
| Duration of anesthesia (min) | 55.04±56.14 | 77.79±61.01 | 12.85 | <0.001 |
| Platelet count ($10^9$/L) | 280.04±90.62 | 253.80±78.63 | 1.46 | 0.004 |
| Platelet volume distribution width (fL) | 11.49±4.51 | 10.42±4.41 | 0.34 | 0.026 |
| Lymphocytes ($10^9$/L) | 3.58±2.05 | 2.97±1.31 | 3.36 | 0.002 |
| Indirect bilirubin (μmol/L) | 5.42±2.59 | 6.27±3.02 | 2.24 | 0.046 |
| Gender, n | | | 0.96 | 0.328 |
| Male | 321 | 70 | | |
| Female | 327 | 85 | | |
| Ocular enucleation, n | | | 0.32 | 0.21 |
| Yes | 48 | 8 | | |
| No | 600 | 147 | | |
| Laterality at diagnosis, n | | | 0.25 | 0.147 |
| Unilateral | 499 | 126 | | |
| Bilateral | 149 | 29 | | |
| Treatment, n | | | 25.05 | <0.001 |
| IVC | 407 | 130 | | |
| IAC | 241 | 25 | | |
| Manage of CIV, n | | | 25.05 | 0.710 |
| Ondansetron | 45 | 2 | | |
| Metoclopramide | 91 | 5 | | |
| Observation | 11 | 1 | | |

CIV, chemotherapy-induced vomiting; RB, retinoblastoma.

**Table 4** Multiple logistic regression analysis of chemotherapy-induced vomiting (N=803)

| Factors | B | AOR (95% CI) | P value |
|---|---|---|---|
| Treatment | | | 0.002 |
| IAC | –0.76 | 0.47 (0.29–0.76) | |
| IVC | | 1 (ref.) | |
| Age (years) | 0.27 | 1.32 (1.11–1.56) | 0.002 |
| Platelet count ($10^9$/L) | –0.003 | 0.997 (0.995–0.999) | 0.017 |

Logistic regression analyses were performed using the backward regression method. B, the regression estimate; IAC, intra-arterial chemotherapy; IVC, intravenous chemotherapy; CI, confidence interval; AOR, adjusted odds ratio.

methods for cancer patients. Clinicians should not only pay attention to the treatment of cancer patients, but also pay attention to the discomfort caused by treatment, timely and properly deal with the side effects of treatment, so as to better ensure the smooth completion of treatment and improve the satisfaction and comfort of patients. However, vomiting caused by chemotherapy is the most painful experience of several patients, which has typically a devastating influence on children and their families, and the cost of hospital resources cannot be ignored (21). The monitoring and control of CIV is still a main challenge. The purpose of this study was to investigate the risk factors of CIV for RB patients.

Based on the previous research data and ethical considerations, ondansetron hydrochloride injection (4 mg: 2 mL) or metoclopramide hydrochloride injection (10 mg: 1 mL) were given to children with vomiting, unless refused by children's parents (22). The data analysis revealed that 143 (92.3%) patients with vomiting received auxiliary antiemetics. There was a statistically significant difference in the incidence of vomiting among children who did not take medicine, ondansetron or metoclopramide, and ondansetron was superior to metoclopramide. Although it is an indisputable fact that the central antiemetics are more reliable than the peripheral antiemetics, this conclusion was at least verified for the first time in the subgroup of RB children receiving arterial/venous chemotherapy. Additionally, the results showed no significant difference in vomiting among the observation, ondansetron, and metoclopramide groups, which might be related to the small sample size (n=12) of the observation group. Meanwhile, 19.3% (155/803) of the patients in this study had vomiting, which was lower than 20.5% reported in the literature (23). This difference suggests that there might be some uniqueness in the physique or treatment of children with RB, and might come from the fact that we only investigated CIV, rather than chemotherapy-induced nausea. Other research teams have reached certain conclusions on their own research objects in studying CINV in children. Moderate or high levels of nausea and vomiting induced by chemotherapy in pediatric patients who aged 6 months to 17 years could be effectively prevented by with or without dexamethasone in ondansetron (24). No matter what the risk factors are, the patients who received carboplatin-based chemotherapy were given triple antiemetic therapy of 5-hydroxytryptamine-3 receptor antagonists, dexamethasone, and neurokinin-1 receptor antagonists (25). The efficacy and safety of these drugs for patients with RB are unclear, indicating the necessity of further research to verify our findings.

Among several methods of CINV intervention, non-drug treatment is also considered to be equally important, and it is necessary to avoid the side effects of antiemetic drugs, especially in young children. Aromatherapy is an effective method to manage POV (26). Systematic desensitization, hypnosis, relaxation techniques, and lorazepam can be considered for the prevention of CINV (12). Numerous therapies are free or cheap, making them a convenient adjunct to medication. Ginger root powder can effectively reduce the severity of acute CINV, as a supplementary therapy to ondansetron and dexamethasone for patients receiving highly carcinogenic chemotherapy (27). The overshadowing technique can reduce the need for antiemetics, which is economic and effective (28).

Older children and those with low platelet count were more likely to vomit than the younger children. The influence of age on CIV remains controversial. Ono *et al.* reported that older age (>5 years old) is an important risk factor for CIV (29). Holdsworth *et al.* demonstrated that vomiting occurs more frequently in children aging under two years old than in older children (30). These differences may result from differences related to respondents. There are reports on high PLT as a protective factor for POV in children undergoing tooth extraction with a deep sedation (18). The narrow age distribution range and the blood parameters distribution of children were similar. Hence, inherent response of the body cannot explain this phenomenon. Although the administration of anesthetics and chemotherapy drugs is strictly based on the body surface area of children and other indicators that can generally summarize a patient's ability to tolerate drugs, group-based differences were found in age, height, and weight. The

results suggested that older children are at a higher risk of vomiting, even though the age-based difference between the two groups is small. Correspondingly, "older children", who received more anesthetics, tolerated longer duration of anesthesia and surgery, which were regarded as the common causes of vomiting.

The results of this study suggested that the chemotherapy regimen was an independent factor influencing CIV in children with RB. The incidence of vomiting in IAC (9.4%) was lower than that in IVC (24.2%). Compared with IVC, IAC includes direct injection of drugs into the tumor tissue, wherein the drug concentration is elevated by 14 times, and the dose is reduced to 1/10 (31). IAC is a relatively new treatment method with a promising curative effect and less toxicity (32). IAC has significantly changed the natural history of RB (33), while it still lacks robust evidence and long-term follow-up (34). Arterial chemotherapy aims to ensure life safety and visual function of the children to eventually establish an evaluable and scalable patient management system to evaluate the safety and effectiveness of IAC from multiple aspects (i.e., strictly monitoring of the most frequently reported ocular complications after IAC, bone marrow suppression, etc.).

### *Strengths and limitations*

This study has two main implications for clinical practice. Firstly, it suggested that CIV of children with RB requires a higher attention, and medical staff should take effective measures to reduce the incidence of vomiting and improve the quality of life of patients. Secondly, at present, there is no consistent conclusion about CIV-associated risk factors. This study showed that age, chemotherapy regimen, and platelet count were risk factors for CIV. Although these risk factors cannot be changed, they can be used to predict whether patients will vomit. Clinical staff should make preventive intervention measures in advance for patients who are at a high risk of vomiting. However, certain limitations should be noted. Firstly, this was a single center study that only investigated the medical history of inpatients admitted to the Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Secondly, the majority of patients were discharged after chemotherapy, thus, the records of delayed nausea and vomiting could not be collected. Thirdly, in this study, patients were not recruited for studying vomiting, and there were objective situations, in which the effective factors could not be completely controlled. Among the 803 cases reviewed in this study, the majority of them were children who were repeatedly hospitalized. Whether CIV differs among RB children with different hospitalization periods should be further studied. Hence, some prospective studies can be designed in the future to recruit patients purposefully, and to verify whether the differences among chemotherapy regimens and results of clinical tests obtained from this study are the decisive factors that can affect CIV, indicating the necessity of developing further predictive interventions.

## Conclusions

RB is the most common primary intraocular malignancy in children. It seriously affects the visual function of children, threatens their life, and causes serious economic and social burden. Vomiting in children during the treatment process not only reduces their quality of life, but also affects the continuity of treatment. This study found that age, chemotherapy regimen, and platelet count were risk factors of CIV in children with RB, and platelet count was the most important predictor of CIV in children with RB. This study was conducted in a single center in China, and the findings should be verified in larger sample populations in different Asian countries.

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## Footnote

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*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the Institutional Review Board of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (approval number SH9H-2019-T291-3). Due to the retrospective nature of this study, informed consent was waived.



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