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Oral 5-aminolevulinic acid administration prior to transurethral resection of bladder tumor causes intraoperative hypotension: Propensity score analysis

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ABSTRACT

Background: Transurethral resection of bladder tumor (TUR-BT) using 5-aminolevulinic acid (5-ALA) is common; however, intraoperative hypotension is frequent. This study aimed to investigate the impact of preoperative oral 5-ALA taking on hypotension and vasopressors dose during general anesthesia, and postoperative nausea and vomiting.

Methods: This retrospective study included patients aged ≥ 20 years who had undergone elective TUR-BT for bladder tumors under general anesthesia. An inverse probability of treatment weighted using stabilized inverse propensity scores was adopted to minimize bias. After adjustment based on patient data, outcomes of interest in patients with and without preoperative administration of 5-ALA were compared using a generalized estimating equation. Primary outcomes were hypotension incidence during anesthesia, which was defined as a mean arterial pressure < 60 mmHg, and the impact of 5-ALA administration on hypotension.

Results: Of 324 patients considered, 153 (47.2 %) received 5-ALA preoperatively. The weighted incidence of hypotension was 23.3 % in patients taking 5-ALA, with an odds ratio of 4.21 (95 % confidence interval 2.07–8.55). Odds ratios (ORs) and 95 % confidence intervals for oral 5-ALA administration were 1.55 (1.23–1.96) for ephedrine, 1.18 (0.66–2.11) for phenylephrine, and 12.3 (5.73–26.5) for postoperative nausea and vomiting.

Conclusions: Preoperative oral 5-ALA administration was associated with hypotension during general anesthesia in patients who underwent TUR-BT despite receiving higher doses of ephedrine. Postoperative nausea and vomiting were also more common in these patients.

1. Introduction

Photodynamic diagnosis assisted transurethral resection of bladder tumor (TUR-BT) using 5-aminolevulinic acid (5-ALA) has facilitated the identification of an accurate resection range and improved oncological outcomes [1–4]. In Japan, preoperative administration of oral 5-ALA was approved in December of 2017.

In aged patients undergoing surgery such as TUR-BT, a strong association exists between intraoperative hypotension and postoperative adverse events, including acute kidney injury, myocardial infarction, and mortality, even if even hypotension occurs only briefly [5,6]. Thus, a recent consensus statement concluded that mean arterial pressures (MAPs) < 60–70 mmHg should be avoided [7]. In contrast, several clinical reports have indicated that intraoperative hypotension is caused by oral administration of 5-ALA before surgery [8–10]. Moreover, some retrospective studies revealed its association with age, body mass index, estimated glomerular filtration rate, and use of antihypertensive drugs; however, the statistical methods used in those studies and the sample size of the studies are insufficient to draw conclusions [11–14].

Given the fact that oral 5-ALA administration is recommended in the 2019 addition of Japanese clinical practice guidelines for bladder cancer [15], it is challenging to conduct randomized control trials to evaluate the impact of oral 5-ALA administration on intraoperative hypotension. Thus, to determine whether oral 5-ALA administration prior to TUR-BT is related to intraoperative hypotension, we retrospectively investigated the incidence of intraoperative hypotension events and assessed the impact of oral 5-ALA administration using propensity scores. Additionally, we examined effects of oral 5-ALA administration on intraoperative

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vasopressor dose and postoperative nausea and vomiting.

2. Materials and methods

2.1. Ethical approval

The protocol of this retrospective study was approved by the Nara Medical University Institutional Review Board, Kashihara, Nara, Japan (Chairperson. M Yoshizumi) on February 5, 2021 (approval number: 2904). The requirement for informed consent was waived owing to the retrospective nature of this study.

2.2. Patient cohort

All patients aged ≥ 20 years who had undergone elective TUR-BT using 5-ALA for bladder tumors under general anesthesia from April 2016 to November 2020 at our tertiary hospital were included in this study. The exclusion criteria applied were as follows: patients who underwent TUR-BT using spinal anesthesia (since mechanisms of hypotension during general and spinal anesthesia differ), patients who required emergency surgery, and those who required procedures in addition to TUR-BT. Finally, patients with insufficient perioperative data were also excluded from the analysis.

2.3. Covariates

Preoperative data including age, sex, body mass index, preexisting medical conditions (hypertension, ischemic heart disease, atrial fibrillation, diabetes), long-term medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium antagonist, β-blocker), serum albumin, serum creatinine, and American Society of Anesthesiologists-Physical Status (ASA-PS) were obtained from electronic medical records. Intraoperative data were also obtained, including anesthetic type (inhalation agents or propofol), fentanyl dose, remifentanil dose, fluid volume, duration of anesthesia, ephedrine dose, phenylephrine dose, blood pressure, and heart rate. Additionally, the occurrence of nausea and vomiting on postoperative day 0 was assessed.

2.4. Patient management

At our institution, all patients undergoing elective surgery were evaluated by anesthesiologists at our preoperative anesthetic clinic, and were instructed to avoid angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the day of surgery. In contrast, anesthesiologist recommend calcium antagonists and β-blocker use be continued on the day of surgery. Additionally, no premedication such as atropine and H2 blocker was given. Patients received 5-ALA(20 mg/kg) 3 h before their surgical procedure, and were allowed to ingest clear liquids for up to 2 h before general anesthesia induction. Intraoperative blood pressure management, including fluid therapy and use of vasopressors, is performed at the discretion of each anesthesiologist. Regarding the use of intraoperative vasoactive drugs, attending anesthesiologists administered ephedrine and phenylephrine as one-shot injections and, if needed, their injections were repeated.

2.5. Primary outcome

The primary outcome assessed in this study was hypotension incidence during anesthesia, which was defined as a MAP value < 60 mmHg, in accordance with a recent review [7]. Additionally, the impact of 5-ALA administration on the incidence of hypotension (< MAP 60 mmHg) was examined.

2.6. Secondary outcomes

The secondary outcome assessed was the impact of 5-ALA administration on the following factors: i) total dose of ephedrine and phenylephrine; ii) incidence of > 80 % MAP reduction prior to administration of 5-ALA, iii) time-integrated value of MAP < 60 mmHg (Fig. 1), iv) time-integrated value of > 80 % MAP reduction from prior to 5-ALA administration. Moreover, the effect of both administration of 5-ALA and the incidence of hypotension during anesthesia on nausea and vomiting on postoperative day 0 was assessed. Furthermore, the effect of 5-ALA on the primary outcome was evaluated by adjusting for ephedrine and phenylephrine dosage. Lastly, blood pressure and heart rate at specific points during the perioperative period were compared with and without preoperative oral administration of 5-ALA.

2.7. Statistical analysis

This was a retrospective study, and, therefore, it was not possible to randomly assign the administration of 5-ALA. Thus, risk factors of patients who did and did not receive 5-ALA may vary. Consequently, an inverse probability of treatment weighted (IPTW) method using stabilized inverse propensity scores was adopted to minimize bias [16].

In randomized controlled trials, the patient's clinical course after assignment is also expected to proceed randomly, with the exception of the outcome. To derive the propensity score for preoperative 5-ALA administration, a logistic regression model was developed. The independent variables considered included age, sex, body mass index, hypertension, ischemic heart disease, atrial fibrillation, diabetes, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium antagonist, β-blocker, serum albumin, serum creatinine, and ASA-PS, types of anesthetics, fentanyl dose, remifentanil dose, fluid volume, and duration of anesthesia. In the model, ASA-PS was divided into two groups: 1 and 2, and 3. Then, ASA-PS 3 was included as a covariate, and inhalation anesthesia was included as a covariate using propofol as a reference.

Standardized mean differences were used to assess the balance of covariates, which was more than 0.1, indicating a lack of balance [17]. Outcomes of interest in patients that did and did not receive 5-ALA preoperatively were then compared using a generalized estimating equation (GEE). All data were analyzed using SPSS (version 22.0; IBM Inc., Armonk, NY, USA) and an RMS package for R, version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria). Differences were considered statistically significant for values of $p < 0.05$. A *t*-test was used to compare blood pressure and heart rate at specific points in the perioperative period (measured at the following 8 points; three hours before surgery (baseline), at admission to the operating room, at the start of anesthesia, at the start of surgery, 30 min after start of surgery, 60 min after start of surgery, 90 min after start of surgery, at the end of anesthesia), and a difference was considered statistically significant if it was less than 0.00625 (0.05/8) due to multiple comparisons.

At our institution, 5-ALA was administered before TUR-BT for the first time in February of 2018. Thereafter, it was administered in 153 of 211 TUR-BT cases that occurred until November 2020. Thus, we decided to enroll cases from April 2016 so an additional 95 that did not receive 5-

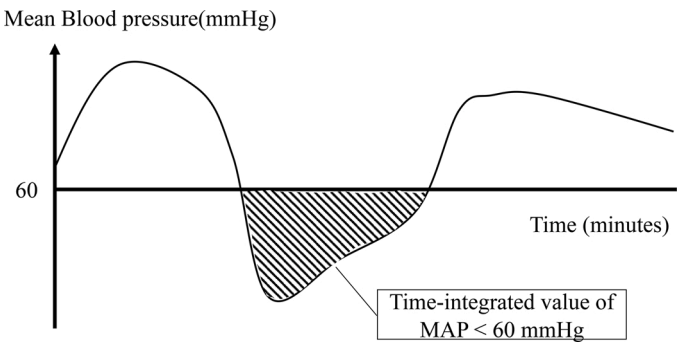

Fig. 1. The explanation of time-integrate value of hypotension.

ALA were included. Since this was a retrospective study with a limited sample size, we determined power (1-β) based on requirements for a type I (α) error of 0.05, effect size of 0.3 (medium effect size), and weighted incidence of MAP < 60 mmHg.

3. Results

Of the 324 patients who underwent TUR-BT under general anesthesia between April of 2016 and November of 2020, 153 (47.2 %) received 5-ALA before surgery. No patients of either group received vasopressors other than ephedrine and phenylephrine and atropine and all had available perioperative data. Unweighted patient data are shown in Table 1. Before inverse probability of treatment weighting, patients taking 5-ALA were more likely to be male, to have atrial fibrillation, and received a greater fluid volume than those who did not receive 5-ALA. Patients taking 5-ALA were also less likely to have ischemic heart disease, receive propofol, and were given an lower average fentanyl dose than those that did not receive 5-ALA. The incidence of the primary outcome of hypotension was 8.1 % (14/171) in patients not given 5-ALA and 25.4 % (39/153) in patients who received 5-ALA. There were no significant differences regarding perioperative data values observed between groups after inverse probability of treatment weighting (Table 2).

3.1. Primary outcome

The weighted incidence of the primary outcome of hypoxia was 7.3 % in patients not taking 5-ALA and 23.3 % in patients taking 5-ALA. Incidence values provided a power of 0.97. Furthermore, GEE revealed that preoperative administration of 5-ALA was associated with an incidence of MAP < 60 mmHg (odds ratio [OR]: 4.21, 95 % confidence interval [CI]: 2.07–8.55) (Table 3). Moreover, postoperatively, no patient required continuous administration of vasopressors and required intensive care unit management.

Table 1
Patient demographics and intraoperative data before IPWT.

	5-ALA(-) (n = 171)	5-ALA(+) (n = 153)	p value	SMD
Age (years)	74.3(9.2)	74.8(9.2)	0.63	0.053
Gender: male	131 (76.6)	130 (85.0)	0.068	0.213
Body mass index (kg/m^2)	23.5 (3.7)	23.58 (3.1)	0.88	0.016
Preexisting medical conditions				
Hypertension	95 (55.6)	88 (57.5)	0.73	0.04
Ischemic heart disease	24 (14.0)	13 (8.5)	0.16	0.176
Atrial fibrillation	9 (5.3)	13 (8.5)	0.27	0.128
Diabetes	52 (30.4)	42 (27.5)	0.62	0.065
Long-term medications				
Angiotensin converting enzyme Inhibitor	6 (3.5)	8 (5.2)	0.58	0.084
Angiotensin Receptor Blocker	46 (26.9)	42 (7.5)	1	0.012
Calcium antagonist	70 (40.9)	59 (38.6)	0.73	0.049
β-blocker	23 (13.5)	17 (11.1)	0.61	0.071
Serum albumin (g/dL)	4.06 (0.4)	4.19 (0.3)	0.005	0.319
Serum creatinine (mg/dL)	1.07 (0.9)	1.26 (1.6)	0.19	0.142
ASA-PS			0.25	0.133
1 or 2	144 (84.2)	121 (79.1)		
3	27 (15.8)	32 (20.9)		
Intraoperative data				
Anesthetics			0.077	0.207
Inhalation agents	159 (93.0)	149 (97.4)		
Propofol	12 (7.0)	4 (2.6)		
Fentanyl (mcg/kg)	2.09(1.3)	1.66(1.1)	0.002	0.351
Remifentanil (mcg/kg)	9.77 (10.0)	9.77 (7.1)	0.99	< 0.001
Fluid volume (mL)	564 (198)	637 (248)	0.004	0.325
Duration of anesthesia (min)	109 (43)	113 (35)	0.38	0.097

Values are reported as means (standardized difference) or numbers (%).
5-ALA, 5-amino levulinic acid; ASA-PS, American Society of Anesthesiologists physical status; IPTW, inverse probability of treatment weighting; SMD, standardized median difference.

Table 2
Mean or percentage after IPWT.

	5-ALA(-)	5-ALA(+)	SMD
Age (years, mean)	74.1	74.3	0.02
Gender: male (%)	82.4	82.9	0.015
Body mass index (kg/m^2, mean)	23.5	23.6	0.039
Preexisting medical conditions			
Hypertension (%)	57.9	56.6	0.025
Ischemic heart disease (%)	11.1	10.5	0.019
Atrial fibrillation (%)	8	7	0.033
Diabetes (%)	28.9	28.6	0.007
Long-term medications			
Angiotensin converting enzyme inhibitor (%)	5.7	4.5	0.052
Angiotensin Receptor Blocker (%)	26.4	27.6	0.025
Calcium antagonist (%)	40.7	39.3	0.029
β-blocker (%)	13.5	12.1	0.044
Serum albumin (g/dL, mean)	4.12	4.16	0.092
Serum creatinine (mg/dL, mean)	1.24	1.17	0.046
ASA-PS			
1 or 2 (%)	79.6	80.8	0.03
3 (%)	20.4	19.2	
Intraoperative data			
Anesthetics			
Inhalation agents (%)	95.5	96.8	0.067
Propofol (%)	4.5	3.2	
Fentanyl (mcg/kg, mean)	1.85	1.85	0.001
Remifentanil (mcg/kg, mean)	9.28	9.26	0.003
Fluid volume (mL, mean)	595	608	0.062
Duration of anesthesia (min, mean)	110	110	0.002

5-ALA, 5-amino levulinic acid; ASA-PS, American Society of Anesthesiologists physical status; IPTW, inverse probability of treatment weighting; SMD, standardized median difference.

3.2. Secondary outcomes

As shown in Table 3, preoperative administration of 5-ALA was associated with an increased total dose of ephedrine (OR: 1.55, 95 % CI: 1.23–1.96), incidence of > 80 % MAP reduction before taking 5-ALA (OR: 2.10, 95 % CI: 1.25–3.53), a time-integrated MAP value < 60 mmHg (OR: 2.42, 95 % CI: 1.59–3.69), and a time-integrated value

Table 3
Association of outcomes with preoperative 5-ALA administration after IPTW.

Outcomes	Odds ratio	95 % Confidence interval	p value
The incidence of < MAP 60 mmHg	4.21	2.07–8.55	< 0.001
Total dose of ephedrine	1.55	1.23–1.96	< 0.001
Total dose of phenylephrine	1.18	0.66–2.11	0.57
The incidence of > 80 % MAP reduction of the MAP before taking 5-ALA	2.10	1.25–3.53	0.005
Time-integrated value of MAP < 60 mmHg	2.42	1.59–3.69	< 0.001
Time-integrated value of > 80 % reduction of the MAP before taking 5-ALA	1.96	1.02–3.77	0.04

5-ALA, 5-amino levulinic acid; IPTW, inverse probability of treatment weighting; MAP, mean arterial pressure.

showing a > 80 % reduction prior to 5-ALA administration (OR: 1.96, 95 % CI: 1.02–3.77). However, total phenylephrine dosage was not associated with 5-ALA administration (OR: 1.18, 95 % CI: 0.66–2.11).

After adjusting for three factors including 5-ALA administration, total dose of ephedrine, and total dose of phenylephrine after IPTW, 5-ALA administration, and total dose of ephedrine remained associated with MAP < 60 mmHg incidence (Table 4). The weighted incidence of postoperative nausea and vomiting was 4.7 % in patients given 5-ALA and 33.8 % in patients that received 5-ALA. As shown in Table 5, 5-ALA administration was positively associated with postoperative nausea and vomiting; however, hypotension was not determined to be an associated factor.

As shown Fig. 2 and Table 6, there was no statistical difference in preoperative blood pressure between two groups (p = 0.80). After admission to the operating room, there was statistically significant differences in blood pressure between the two groups, except before the start of anesthesia (p = 0.037) and 90 min after the start of surgery (p = 0.64). Heart rate showed a statistically significant difference at all measurement points except baseline (p = 0.53) (Fig. 3 and Table 6).

4. Discussion

This study showed that the weighted incidence of hypotension during anesthesia was 23.3 % in patients taking 5-ALA prior to TUR-BT, and patients receiving 5-ALA were 4.2 times more likely to experience hypotension than those who did not receive 5-ALA. The effect of 5-ALA on hypotension persisted after adjusting for ephedrine and phenylephrine dosage. Additionally, preoperative oral 5-ALA administration affected hypotension events defined by various criteria, and the total dose of ephedrine administered; however, there was no association between preoperative oral 5-ALA administration and total phenylephrine dose. Moreover, patients who were given 5-ALA were more likely to experience postoperative nausea and vomiting than those who were not, regardless of intraoperative hypotension incidence.

Previous exploratory studies have reported several factors associated with the hypotension that occurs after oral 5-ALA administration [11–14]. However, the goodness of fit and c-statistics of the logistic regression model to derive the results have not been assessed. In addition, the statistical validity of the model was questioned due to the large number of explanatory variables entered into the model, which resulted in overfitting. In addition, no study has ever investigated the effect of oral 5-ALA post-treatment on hypotension, adjusting for patient background. Therefore, in this retrospective study, we used IPTW to adjust for bias and calculate power, but I think our method makes sense because RTC is difficult.

In the literature, the reported incidence of hypotension during anesthesia in TUR-BT using 5-ALA varies from 6.3%–70% [11–14]. Observed differences may be due to different definitions of hypotension applied, different study cohorts, and use of varied anesthetic techniques. In this study, hypotension was defined using a mean blood pressure values, which determines organ perfusion. The definition was based on a recent consensus statement, and time-integrated values were also evaluated to assess the effect of time [7]. Moreover, only patients undergoing TUR-BT who were placed under general anesthesia were included in the analysis because the mechanism of hypotension in patients placed under general anesthesia differs from those that receive spinal anesthesia, which causes rapid sympathetic blocks. As a result, preoperative oral 5-ALA administration effects hypotension, defined as various criteria during anesthesia. The precise reasons preoperative oral 5-ALA administration increased hypotension incidence remain unclear; however, it has been suggested that protoporphyrin IX, which results from the oral administration of 5-ALA, decreases systemic and pulmonary vascular resistance [18]. Moreover, the vasodilation and depression of myocardial contractility caused by anesthetics results in hypotension and a compensatory mechanism to increase heart rate to maintain systemic blood pressure. Analysis of blood pressure and heart rate at specific points in the perioperative period revealed that patients taking oral 5-ALA preoperatively had a higher heart rate after anesthetic induction compared to patients not taking oral 5-ALA. The exact reason for this is unknown, but higher heart rate might be compensation for the severe decrease in vascular resistance. To clarify these mechanisms, it is necessary to keep arterial pressure lines and central venous catheters to measure cardiac output and vascular resistance, and future studies are expected.

Although the average total dose of phenylephrine administered both groups considered did not significantly differ, the total dose of ephedrine given to patients taking 5-ALA was greater than that which was given to patients who did not receive 5-ALA. Furthermore, preoperative oral 5-ALA administration and total dose of ephedrine were associated with hypotension, even after adjustment using IPTW. These findings likely indicate that attending anesthesiologists preferred ephedrine rather than phenylephrine to manage patient blood pressure. However, use of ephedrine was not sufficient, and future studies are needed to improve the effectiveness of vasopressor use.

Although the mechanism of postoperative nausea and vomiting remains incompletely clarified, serotonin and the sympathetic nervous

Table 4
Association of the incidence of < MAP 60 mmHg adjusting 5-ALA administration, total dose of ephedrine and total dose of phenylephrine after IPTW.

Covariates	Odds ratio	95 % Confidence interval	p value
5-ALA administration	2.77	1.29–5.92	0.008
Total dose of ephedrine	1.09	1.04–1.14	< 0.001
Total dose of phenylephrine	1.49	0.30–7.41	0.62

5-ALA, 5-aminolevulinic acid; IPTW, inverse probability of treatment weighting; MAP, mean arterial pressure.

Table 5
Association of the postoperative nausea and vomiting adjusting 5-ALA administration and the incidence of MAP < 60 mmHg after IPTW.

Covariates	Odds ratio	95 % Confidence interval	p value
5-ALA	12.3	5.73–26.5	< 0.001
The incidence of MAP < 60 mmHg	0.62	0.28–1.39	0.25

5-ALA, 5-amino levulinic acid; IPTW, inverse probability of treatment weighting; MAP, mean arterial pressure.

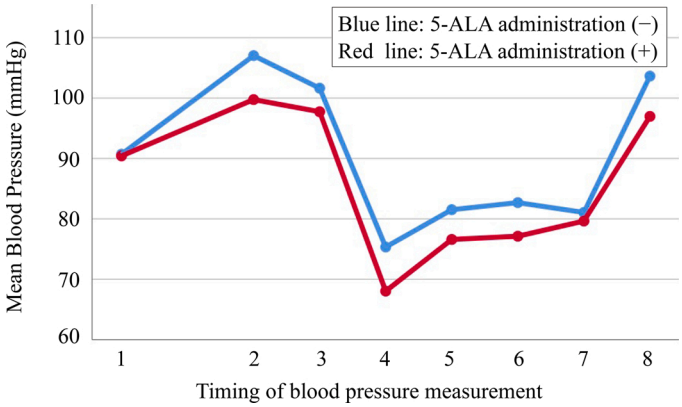

Fig. 2. The change in blood pressure over time.
The timing of the measurements indicated by each number is as follows: 1 is three hours before surgery (baseline), 2 is at admission to the operating room, 3 is at the start of anesthesia, 4 is at the start of surgery, 5 is 30 min after start of surgery, 6 is 60 min after start of surgery, 7 is 90 min after start of surgery, 8 is at the end of anesthesia.

Table 6
The value of blood pressure and heart rate over time.

Parameter	Timing of measurement	5-ALA(-)	5-ALA (+)	p value
Blood pressure (mmHg)	Three hours before surgery (baseline)	90.7 (9.1)	90.4 (10.6)	0.80
	At admission to the operating room	107.0 (15.1)	99.7 (13.5)	<0.001
	At the start of anesthesia	101.6 (18.0)	97.7 (15.1)	0.037
	At the start of surgery	75.3 (12.9)	68.0 (12.6)	<0.001
	30 min after start of surgery	81.5 (15.6)	76.5 (15.3)	0.005
	60 min after start of surgery	82.6 (14.3)	77.1 (14.7)	0.004
	90 min after start of surgery	81.0 (14.6)	79.6 (18.2)	0.64
	At the end of anesthesia	103.6 (16.6)	96.9 (18.5)	0.001
Heart rate(bpm)	Three hours before surgery (baseline)	70.9 (10.7)	70.2 (9.7)	0.53
	At admission to the operating room	76.4 (15.5)	82.0 (15.9)	0.001
	At the start of anesthesia	73.6 (14.7)	81.2 (16.4)	<0.001
	At the start of surgery	61.8 (12.2)	72.0 (12.8)	<0.001
	30 min after start of surgery	63.7 (14.5)	74.3 (13.0)	<0.001
	60 min after start of surgery	62.6 (13.6)	74.5 (11.9)	<0.001
	90 min after start of surgery	63.3 (15.0)	74.5 (12.5)	<0.001
	At the end of anesthesia	77.7 (15.8)	86.2 (16.5)	<0.001

Values are reported as means (standardized difference).
5-ALA, 5-amino levulinic acid.
The number of patients were different in each measurement timing. Three hours before surgery (baseline), at admission to the operating room, at the start of anesthesia, at the start of surgery, and at the end of anesthesia, 171 patients who did not received5-ALA and 153 patients who received 5-ALA were included. At 30 min after start of surgery, 60 min after start of surgery, and 90 min after start of surgery, 165 patients who did not received 5-ALA and 152 patients who received 5-ALA, 113 patients who did not received 5-ALA and 117 patients who received 5-ALA, and 54 patients who did not received 5-ALA and 64 patients who received 5-ALA were included, respectively.

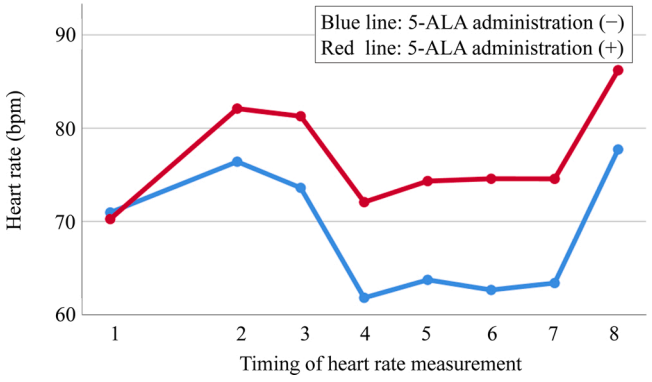

Fig. 3. The change in heart rate over time.
The timing of the measurements indicated by each number is as follows: 1 is three hours before surgery (baseline), 2 is at admission to the operating room, 3 is at the start of anesthesia, 4 is at the start of surgery, 5 is 30 min after start of surgery, 6 is 60 min after start of surgery, 7 is 90 min after start of surgery, 8 is at the end of anesthesia.

system are recognized as important pathways. Hypotension prompts the release of serotonin, which results in increases in serotonin levels [19]. In addition, an elevated concentrations of serotonin prevent the removal of serotonin from the blood, which further increases serotonin levels, and consequently, nausea and vomiting [20]. Although postoperative nausea and vomiting were more commonly observed in patients who received oral 5-ALA before surgery, hypotension during anesthesia was not a significant factor. The documented incidence of nausea and vomiting in the package insert of 5-ALA is 6.5–7.3 % [21]. Further, 5-ALA and protoporphyrin IX may have a greater impact on postoperative nausea and vomiting than hypotension during anesthesia; however, the precise mechanism by which the compounds affect hypotension remains unknown.

This study has some limitations. First, patient data were adjusted using IPTW to minimize bias; however, some data known to influence hypotension during anesthesia, such as preoperative fluid management, were not available. Second, the generalizability of our findings may be limited since this was a single-center study. Finally, intraoperative management depended on the attending anesthesiologist; thus, results may differ if a standardized management strategy is applied.

In conclusion, preoperative oral 5-ALA administration was associated with hypotension during anesthesia in patients who underwent TUR-BT under general anesthesia despite receiving a higher average dose of ephedrine. Postoperative nausea and vomiting were more common in patients taking oral 5-ALA before surgery, regardless of hypotension status during anesthesia.

Declaration of Competing Interest

The authors report no declarations of interest.

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