Medication administration time: an independent risk predictor for hypotension after induction of general anaesthesia for non-cardiac surgery: a retrospective observational study

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Abstract

Background: Hypotension following induction of general anaesthesia (GAIH) is common, and it's associated with adverse outcomes. Although demographic and dose-related factors have been investigated, it is unknown whether administration time has an effect.

Methods: Our analysis included 142 individuals who underwent elective otorhinolaryngologic procedures between March 1, 2017 and August 31, 2017. Under intravenous anaesthesia, patients were intubated using a single lumen endotracheal tube. The occurrence of GAIH, defined as a 30% decline in MAP from baseline, was recorded, and the risk variables for GAIH, including demographical, dose-related, and time-related factors, were investigated.

Results: The final analysis includes 123 of the 142 participants that were enrolled in our trial. GAIH occurred 15.45 percent of the time between entering the operating room and intubation, and 55.28 percent of the time between intubation and the commencement of surgery. Propofol's time to peak effect ($P_{propofol}$) (less than -0.4 min or more than 0.6 min) was associated with a lower risk of GAIH (OR 0.354, 95 percent CI, 0.142–0.884, p=0.026).

Conclusions: Medication administration, especially $P_{propofol}$, is a risk factor for GAIH.

Trial registration: Chinese Clinical Trial Registry, registered 04/05/2021 - Retrospectively registered, http://www.chictr.org.cn/edit.aspx?pid=125840&htm=4

Introduction

With a prevalence of over 60%, hypotension following general anaesthesia induction (GAIH) can occur during both elective and emergency surgery. K. Maheshwari et al. discovered that GAIH is associated with postoperative acute kidney injury during non-cardiac surgery, while Robert et al. discovered that GAIH in the vascular surgery is associated with adverse outcomes such as prolonged ICU stay, postoperative ventilation, and mortality [1–4]. At certain times, the risk of stroke increased with each minute of hypotension (a drop of more than 30% in mean arterial pressure from baseline) [5].

GAIH has been investigated as a predictor, with results varying between studies [2, 6–8]. Demographic and dose-related factors have been reported to be significant. However, in routine practice, we observe that a rapid bolus of induction agents frequently results in a significant decrease in blood pressure; however, it is unknown whether the time required to administer induction agents has an effect on the occurrence of GAIH.

As a result, in addition to demographic and dose-related variables, we're interested in determining whether there is a relationship between time and GAIH in our research.

Methods

This study was approved by the ethics committee of West China Hospital (approval number: 2017 – 434) and registered with the Chinese Clinical Trial Registry (registration number: chiCTR2100046109). This study was performed in accordance with the Declaration of Helsinki, patients who underwent elective otorhinolaryngology surgery at West China Hospital under general anaesthesia with endotracheal intubation between March and August 2017 were included in the study (Table 1).

Table 1
Demographic and clinical characteristics of patients undergoing IV induction

variable	All patients		
	NP(n = 53)	GAIH(n = 70)	p
Age(year)			0.106
≤ 65	50(94.4)	61(85.9)	
＞65	3(5.7)	10(14.1)	
Gender			0.800
Male	23 (43.4)	33 (46.5)	
Female	30 (56.6)	38 (53.5)	
ASA			0.103
I ~ II	45(84.9)	66 (94.3)	
III ~ IV	8(15.1)	4 (5.7)	
BMI(kg/m^2)			0.647
BMI ≤ 24	42 (79.2)	53 (75.7)	
BMI＞24	11 (20.8)	17 (24.3)	
Hypertension	6(11.3)	11 (15.7)	0.488
diabetes	2(3.8)	4 (5.7)	0.624
CHD	1(1.9)	1 (1.4)	0.844
Smoking	5(9.4)	7 (10.0)	0.917
Drinking	4(7.5)	4 (5.7)	0.686
Baseline MAP	85.17(12.67)	85.89(17.14)	0.790
PreECG			0.068
Normal	50(94.3)	59 (84.3)	
Premature		2 (2.9)	

CHD: chronic heart disease; $D_{sufentanil}$: dose of sufentanil; $D_{midazolam}$: dose of midazolam; $T_{propofol}$: administration time of propofol; $T_{sufentanil}$: administration time of sufentanyl; $T_{midazolam}$: administration time of midazolam; $P_{propofol}$: peak effect time of propofol; $P_{sufentanil}$: peak effect time of sufentanil; $P_{midazolam}$: peak effect time of midazolam

* denotes statistical significance compared with NP group ($P < 0.05$)

variable	All patients		
	NP(n = 53)	GAIH(n = 70)	p
Bradycardia	1(1.9)	1 (1.4)	
Tachycardia		2 (2.9)	
ST-T change	1(1.9)	5 (7.1)	
Dpropofol (mg/kg)	2.20(0.72)	2.15 (0.65)	0.575
Dsufentanil (ug/kg)	0.30(0.12)	0.24 (0.15)	0.041*
Dmidazolam (mg/kg)	0.037(0.10)	0.034 (0.0078)	0.224
Tpropofol	-4.13 (1.78)	-3.27 (1.69)	0.007*
Tsufentanil	-4.64 (1.68)	-3.84 (1.44)	0.005*
Tmidazolam	-5.12(1.71)	-4.62(1.12)	0.089
Ppropofol	-2.51 (1.86)	-1.61 (1.68)	0.006*
Psufentanil	0.37 (1.66)	0.43 (1.68)	0.823
Pmidazolam	-2.44(1.68)	-1.55(1.40)	0.006*
Maintain			0.001*
No	9 (17.0)	31 (44.3)	
Inhalational	19 (35.8)	22 (31.4)	
Intravenous	10 (18.9)	10 (14.3)	
Inhalational + Intravenous	15 (28.3)	7 (10.0)	
CHD: chronic heart disease; $D_{sufentanil}$: dose of sufentanil; $D_{midazolam}$: dose of midazolam; $T_{propofol}$: administration time of propofol; $T_{sufentanil}$: administration time of sufentanyl; $T_{midazolam}$: administration time of midazolam; $P_{propofol}$: peak effect time of propofol; $P_{sufentanil}$: peak effect time of sufentanil; $P_{midazolam}$: peak effect time of midazolam			
* denotes statistical significance compared with NP group ($P < 0.05$)			

Nineteen individuals were excluded from our trial because of inhalational induction, large dosage opioid-benzodiazepine induction, local nerve blockade anaesthesia before induction, or unsuccessful intubation or difficult airway (Fig. 1). In compliance with the privacy policy, patient anaesthetic records were recorded using the Patient Data Management and Review system (mindray corporation, USA).

The primary endpoint in our investigation was the development of GAIH, which was defined as a drop in MAP of more than 30% from baseline [2], whereas a change in MAP of less than 30% was classified as normal blood pressure (NP). The baseline data for MAP were collected from the time the patient entered the operating room until induction began, and records were only included in our study if the MAP was monitored every 1 minute.

Demographical, dose-related, and time-related risk factors for GAIH were categorised. ASA classification, age, gender, BMI, and medical history were all used as demographic factors. In our investigation, anaesthesia was inducted using propofol, sufentanil, midazolam, cisatrocurum, or rocuronium, and dose-related predictors were standardized to body weight and divided into groups according to clinical dose range.

The peak effect time of administering drugs was used to define time-related predictors. To describe the time points (Fig. 2), we defined the start of induction as the first administration of induction drug and the end of induction as 15 minutes after the last intravenous injection (or the end of recording with the onset of surgery), dividing the induction into intervals 1 and 2 by intubation. Furthermore, we set the time of intubation to “0” minute, so the agents used before or after intubation were recorded as $T_{anesthetics}$ with positive or negative values (e.g. $T_{anesthetics}$=-2 min means a drug was given 2 minutes before intubation, and this period belongs to interval 1), and $P_{anesthetics}$ was calculated based on the peak effect time of Tanesthetics (e.g. $T_{propofol}$=-2 min, $P_{propofol}$=$T_{propofol}$+1.6 min=-0.4 min, means if propofol was given 2 min before intubation, the peak effect of propofol was suggested to reach 0.4 min before intubation)[9].

2.1. Sample size calculation and statistical analysis

NCSS PASS version 11.0 (NCSS LLC, Kaysville, Utah, USA) was used to compute sample size, which was based on a target number of 10 outcome occurrences per independent variable [10]. SPSS software version 23.0 was used for statistical analysis (IBM Corp., Armonk, NY, USA). Logistic regression modeling was used to analyze the effect of variables on the risk factors for GAIH.

Based on a two-tailed significance threshold of 0.05 (estimated 70–90% incidence of GAIH)[10], at least 92 patients [4] were estimated to discern the difference with 90% power. A multiple logistic regression model with 6 or less predictor variables was thus allowed.

Before logistic regression, continuous variates were categorized according to the least hemodynamic changes[11–14]. Continuous data were first reported as mean (SD) or median (interquartile range), as appropriate, and the difference between groups were analyzed using the Manne-Whitney U test. The categorical data were presented as proportion percentages and were analyzed using the $\chi 2$ test or Fisher’s exact test. Variables with $p < 0.05$ in the univariate analysis were subsequently allocated in a multivariate binary logistic regression mode testing. Multicollinearity were assessed between independent risk factors by using variance inflation factors (VIF) with a reference value of 10. Risk factors was confirmed by the backward LR method in both univariate and multivariate logistic regression. Results of

logistic regression analysis was presented as odds ratio (OR) with 95% confidence intervals (CI), the level of significance was $P < 0.05$.

Results

3.1. Patient population

In our study, a total of 142 patients undergoing elective ENT surgery were evaluated, with 19 patients being excluded (Fig. 1). GAIH occurred in 43.1% (70/123) of patients during induction: in interval 1, GAIH occurred in 15.45% (19/123), and in interval 2, GAIH occurred in 55.28% (68/123) of patients. Demographic information and peri-inductive characteristics were presented (Table 1). There was no statistical difference in demographic data or medical history between Group NP and Group GAIH. While there were differences in dose-related and time-related data between patients with GAIH and those who did not have GAIH. Sufentanil dose in group GAIH was 0.24 ± 0.15 μg/kg, which was lower than that in group NP (0.3 ± 0.12 μg/kg, p=0.041). $P_{propofol}$ in group GAIH (-1.61 ± 1.68 min) was closer to intubation (p=0.006) than in group NP ($P_{propofol}$=-2.51 ± 1.86 min) (p = 0.006).

3.2. Risk factors associated with GAIH

In intervals 1 and 2, possible risk factors for GAIH are illustrated (Tables 2 and 3). ($P_{midazolam}$ isn't included in logistic regression because it hasn't been related to hemodynamic changes [14]). When GAIH was selected as the dependent variable, univariate analysis showed that the maintenance technique, $P_{propofol}$, and $P_{sulfentanil}$ were significantly associated with GAIH in interval 2 ($p < 0.05$) (Table 3); however, no risk was observed to be associated with GAIH in interval 1.

After the multicollinearity test, all three variables were included in interval 2 (VIF < 10, $P > 0.05$). Multivariate logistic regression analysis first identified none independent predictors of GAIH with three variables, and results of the Hosmer-Lemeshow test revealed a good fit of the model ($\chi2$=0.713, df = 3, p=0.87). $P_{propofol}$ (less than − 0.4 min or more than 0.6 min) was significantly associated with a decreased risk of GAIH (OR 0.354, 95% CI [0.142–0.884], P=0.026) (Table 3), and the Hosmer-Lemeshow test revealed a good fit of the model ($\chi2$=1.195, df=2, p=0.55) when the maintain method was excluded from the model (Table 3).

Table 2

Univariate and multivariate analyses associated with GAIH during Period 1.

variable	Univariate analysis		Multivariate analysis	
n=19	OR (95%CI)	p	OR (95%CI)	p
Age(year)	1.762 (0.437-7.111)	0.426	-	-
Gender	0.881 (0.331-2.348)	0.800	-	-
ASA	1.106 (0.222-5.498)	0.902	-	-
Hypertension	1.867 (0.537-6.494)	0.326	-	-
diabetes	1.100(0.121-9.977)	0.932	-	-
Smoking	0.470 (0.057-3.868)	0.482	-	-
Drinking	0.770 (0.089-6.641)	0.812	-	-
Baseline MAP 70mmHg	3.273 (0.408-26.273)	0.265	-	-
Maintain method			-	-
No (reference)			-	-
Yes	1.052 (0.368-3.009)	0.924	-	-
Dpropofol (mg/kg)			-	-
2-2.5 reference				-
2 or 2.5	3.092 (0.961-9.949)	0.058		-
Dsufentanil (ug/kg)			-	-
0.1-0.3				-
0.1 or0.3	2.162 (0.587-7.966)	0.246		-
Ppropofolmin			-	-
-0.4 – 0.6reference				-
-0.4 or 0.6	2.705 (0.738-9.911)	0.133		-
Psufentanil			-	-
-0.4 – 0.6reference				-
-0.4 or 0.6	0.697 (0.257-1.891)	0.479		-

CHD: chronic heart disease; $D_{sufentanil}$: dose of sufentanil; $P_{propofol}$: peak effect time of propofol; $P_{sufentanil}$: peak effect time of sufentanil

* denotes statistical significance (P<0.05) in the logistic regression analysis.

Table 3

Univariate and multivariate analyses associated with GAIH during Period 2.

variable	Univariate analysis		Multivariate analysis	
n=68	OR (95%CI)	p	OR (95%CI)	p
Age(year)	2.989 (0.780-11.452)	0.110	-	-
Gender	1.056 (0.517-2.157	0.882	-	-
ASA	0.367 (0.104-1.292	0.119	-	-
Hypertension	1.182(0.418-3.341)	0.752	-	-
diabetes	1.656 (0.292-9.398)	0.569	-	-
CHD	0.806(0.049-13.186)	0.880	-	-
Smoking	1.148 (0.343-3.837	0.823	-	-
Drinking	0.797 (0.190-3.343	0.756	-	-
Baseline MAP	0.467(0.154-1.417)	0.179	-	-
Maintain method				
No (reference)				
Yes	0.281(0.122-0.649)	0.003	0.562(0.183-1.722)	0.313
Dpropofol (mg/kg)			-	-
2-2.5 reference				
2 or 2.5	0.682 (0.329-1.412)	0.303		
Dsufentanil (ug/kg)			-	-
0.1-0.3				
0.1 or 0.3	1.042 (0.467-2.322)	0.920		
Ppropofol min				
-0.4 – 0.6 reference				
-0.4 or 0.6	0.263 (0.111-0.622)	0.002*	0.354(0.142-0.884)	0.026*
Psufentanil				
-0.4 – 0.6 reference				
-0.4 or 0.6	3.134(1.451-6.771)	0.004*	2.241(0.983-5.107)	0.055

CHD: chronic heart disease; $D_{sufentanil}$: dose of sufentanil; $P_{propofol}$: peak effect time of propofol; $P_{sufentanil}$: peak effect time of sufentanil

* denotes statistical significance (P<0.05) in the logistic regression analysis.

Discussion

The goal of this retrospective study was to see if a time-related variable is a risk factor for GAIH, and medication administration time was found to be an independent predictor of GAIH.

In our study, $P_{propofol}$ is the only risk factor of medication administration time for GAIH in our study. (Pmidazolam isn't included in logistic regression because it hasn't been linked to hemodynamic changes[14]). $P_{propofol}$ represents the time difference between propofol peak effect and intubation; less than − 0.4 min or more than 0.6 min of $P_{propofol}$ represents a significant effect (OR = 0.352), indicating that if propofol reached peak effect earlier than 0.4 min before intubation or later than 0.6 min after intubation, there is a lower chance of GAIH developing. Despite the fact that propofol use is a predictor of GAIH[15], the dose-related effect of propofol appears to be of no importance in our investigation when compared to the time-related effect. Various factors have been identified as predictors of GAIH, including baseline MAP greater than 70 mmHg, age greater than 50 years, the use of propofol for anaesthesia induction, and increasing fentanyl induction dose, and a high BMI is considered a risk factor for intraoperative hypotension in children[2] [4]. Since the studies described were retrospective studies with considerable differences in demographic and clinical parameters (such as age, ASA classification, medical history, and surgery time), these differences may result in various risk factors[2] [4] [15, 16].

Despite the fact that intraoperative hypotension has been attributed to an increased risk of postoperative non-fatal stroke [17], and the risk of stroke increased at specific times for every minute of hypotension (a drop in mean arterial pressure of more than 30% from baseline) [5]. Some researchers believe that a 15-minute interval is too short to affect surgical outcomes, and that hypotension is common in surgery and can be easily corrected with vasoactive agents. As a result, the importance of GAIH has been undervalued for a long time[18, 19].

Though some anesthesiologists consider that hypotension in such a short period of time can be effectively managed with no serious postoperative consequences, the strong correlation between GAIH and unfavorable effects has steadily been confirmed[2, 5, 20, 21]. We should also note that our attention is relatively poor between intubation and the start of surgery, as evidenced by handwritten anesthetic workloads or computer-system records [22], and that monitoring intervals are usually longer than the intubation duration. All of the above factors interact to enhance the likelihood of hypotension being overlooked.

Despite our best efforts, there are some limitations in our research. The data in our study have uncontrolled confounding biases because it is a retrospective observational study, for example, whether GAIH is a result of using maintenance medications. These factors, however, were found to have no

connection with GAIH following multivariate analysis. Despite the fact that the sample size in our study is sufficient to perform a logistic regression, it is still insufficient to explain the various anaesthesia administration conditions, as the kind and dose of drugs changes between hospitals and nations. And our findings can only be interpreted as a relationship between limited drug usage and elective surgery at our institution. As a result, more research is needed to analyze large databases of elective and emergency procedures.

Therefore, $P_{propofol}$ is a risk factor for GAIH from intubation to the start of operation.

Abbreviations

GAIH
hypotension after induction of general anaesthesia
CHD
chronic heart disease
$D_{sufentanil}$
dose of sufentanil
$D_{midazolam}$
dose of midazolam
$T_{propofol}$
administration time of propofol
$T_{sufentanil}$
administration time of sufentanyl
$T_{midazolam}$
administration time of midazolam
$P_{propofol}$
peak effect time of propofol
$P_{sufentanil}$
peak effect time of sufentanil
$P_{midazolam}$
peak effect time of midazolam

Declarations

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Abbreviations

GAIH: hypotension after induction of general anaesthesia; CHD: chronic heart disease; $D_{sufentanil}$: dose of sufentanil; $D_{midazolam}$: dose of midazolam; $T_{propofol}$: administration time of propofol; $T_{sufentanil}$: administration time of sufentanyl; $T_{midazolam}$: administration time of midazolam; $P_{propofol}$: peak effect time of propofol; $P_{sufentanil}$: peak effect time of sufentanil; $P_{midazolam}$: peak effect time of midazolam

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the institutional restrictions but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective cohort study was approved (approval number: 2017-434) by ethics committee of West China hospital, the ethics committee waived the need for written informed consent from patients because all patients were not subjected to research activities. This study was performed in accordance with the Declaration of Helsinki.

Competing interests

All authors declare no competing interests.

Consent for publication

Not applicable

Authors' contributions

YY design the study, acquire and analyze the data, and write the article.

WSZ supervise the study and data analysis, and revise the article.

QH acquire and analyzed the data. All authors read and approved the final manuscript.

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Figures

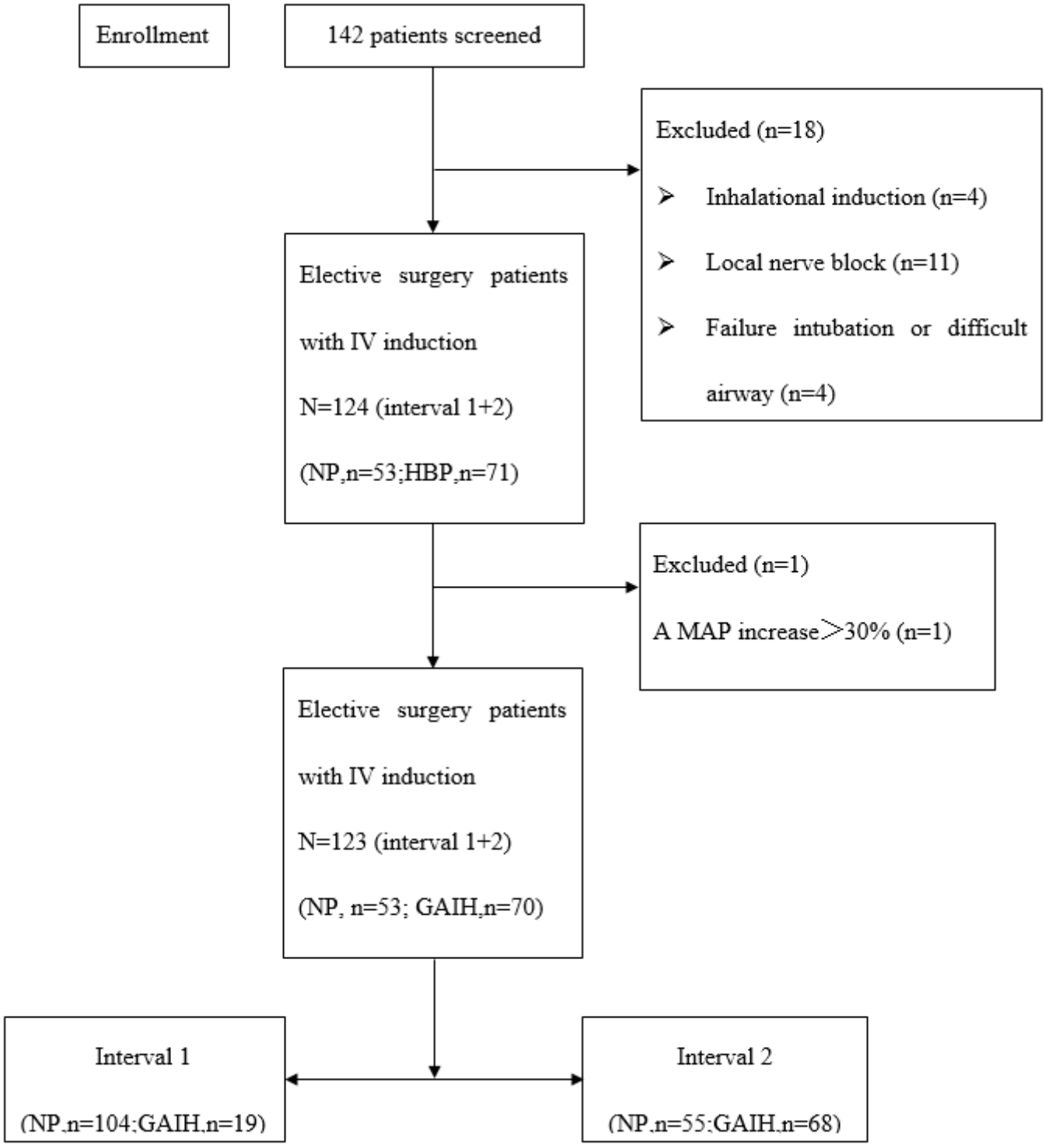

Figure 1

Flow chart of the study. A total of 142 patients under elective ENT surgery were allocated in study, after exclusion of 19 patients, 123 patients were analyzed. The incidence of GAIH during induction time was 43.1% (70/123): in interval 1, the incidence of GAIH was 15.45% (19/123); in interval 2, the incidence of GAIH was 55.28% (68/123).

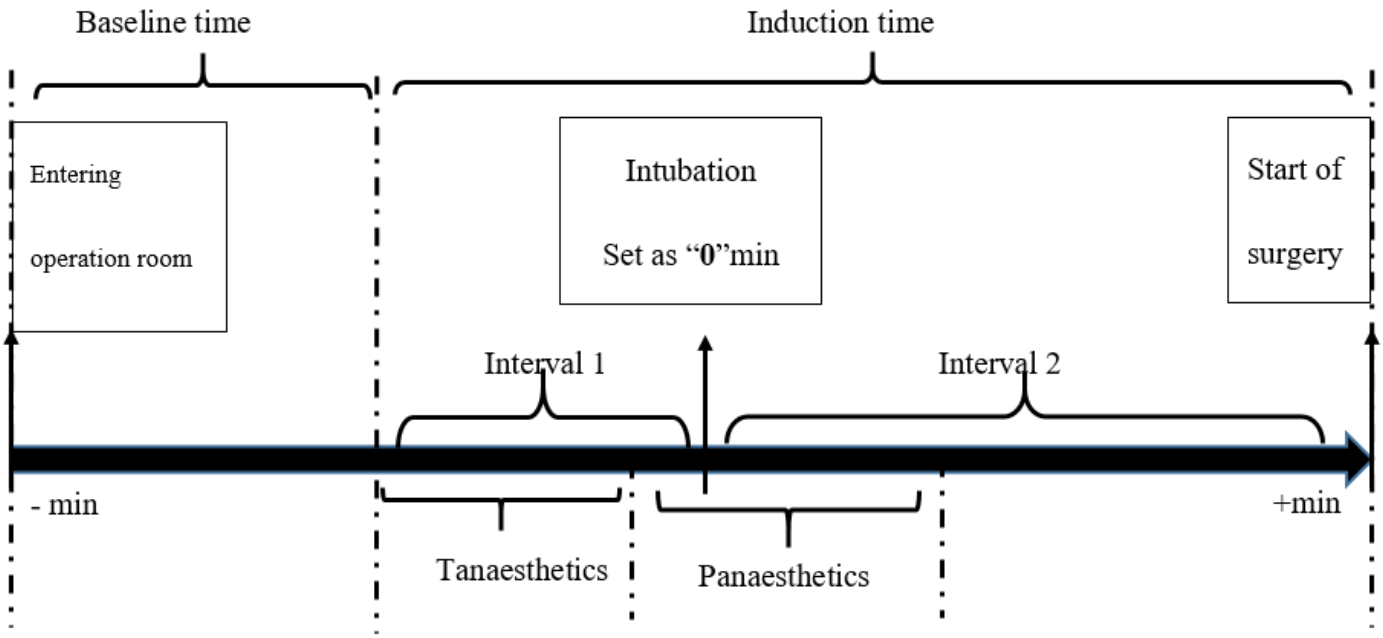

Figure 2

Definitions of intervals. Induction time was measured from the first administration of induction drug to 15 minutes after the last intravenous injection completed (or stop recording with the onset of surgery), which was divided into interval 1 and interval 2 by the onset of intubation. The onset of intubation was set as "0" minute. $T_{anaesthetics}$: administration time of drugs; $P_{anaesthetics}$: peak effect time of anaesthetics.