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Factors influencing intraoperative bradycardia in adult patients

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Abstract
Purpose. In order to elucidate the prominent factors involved in intraoperative bradycardia in adult patients, we retrospectively investigated the association between the potential risk factors and intraoperative bradycardia, using multiple logistic regression.
Methods. The perioperative records for 499 adult patients who had undergone any of six elective surgeries were retrospectively examined. The potential factors included patient characteristics, the use of perioperative drugs for anesthesia, and the types of operational procedures. Heart rates were extracted at five points perioperatively. The frequencies and total doses of atropine injections to treat bradycardia were examined. Simple and multiple logistic regressions were used to analyze the relative risk factors for a intraoperative bradycardia.
Results. The multiple logistic regression analysis revealed that the absence of atropine premedication was the most prominent risk factor for bradycardia (odds ratio; 1.86–5.51) from arrival in the operating room until the end of the operation. Other prominent factors, whose effects were only temporary, were as follows. Males had a higher risk of bradycardia than females upon arrival in the operating room. Surgical procedures with an epidural or subarachnoid blockade tended to have a higher risk for bradycardia after the operation. Propofol induction had a greater risk for bradycardia than thiopental after the end of the operation. Endotracheal intubation had a lower risk for bradycardia than no endotracheal intubation after induction. Vecuronium tended to induce bradycardia after operation.
Conclusion. The most prominent factor affecting heart rate was atropine premedication. It was noteworthy that a single preoperative administration of atropine affected heart rate throughout the operation.

Key words Bradycardia · Anesthesia · Atropine · Premedication

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Introduction

Control of heart rate is suggested to be beneficial to prevent perioperative cardiac events [1]. Although anesthesiologists are nervous about tachycardia, bradycardia is often induced by anesthetics and sometimes has to be treated. Widely used anesthetics, such as propofol, fentanyl and the muscle relaxant, vecuronium bromide, reduce heart rate, and occasionally induce bradycardia [2]. Neuroaxial anesthesia also induces bradycardia [3–5]. Although bradycardia itself rarely progresses to cardiac arrest, bradycardia is not beneficial for patients with cardiac valve regurgitation, and occasionally progresses to cardiac arrest in cardiac-compromised patients. Bradycardia is still an undesirable event; hence, it is worthwhile to analyze risk factors for intraoperative bradycardia. Therefore, we retrospectively examined putative perioperative risk factors for bradycardia, using multivariate logistic regression models, and we discuss the factors influencing intraoperative heart rate.

Patients and Methods

We retrospectively examined the perioperative records of 499 patients over 16 years of age who had undergone any of six elective surgical procedures from August 2001 to December 2002 at the Federation of National Public Service Personnel Mutual Aid Associations, Tachikawa Hospital. This type of statistical retrospective analysis of patient records was allowed by the ethics committee without the need to obtain the committee's approval. The surgical procedures included mastectomy, abdominal procedures, transurethral resection (TUR), laparoscopic cholecystectomy (LAP-C), and orthopedic procedures with or without regional blockade. Patients with an American Society of Anesthesiologists (ASA) physical status of more than 3 were excluded from the study.

Although the conventional premedication has been intramuscular atropine and meperidine injection 30 min prior to the patient's arrival in the operating room, recently atropine has been often withheld from the routine premedication. In our study, the final decision on premedication was made by the anesthesiologists who performed the preoperative rounds. In most gynecological surgeries, atropine was not given. On the other hand, atropine was given for most of the otolaryngological surgeries. These gynecological and otolaryngological patients were excluded from the retrospective study in order to avoid statistical bias. We then chose six types of surgical procedures in which atropine premedication is still controversial. Thus, the ratios of premedication with and without atropine were comparable.

All patients were given 150 mg ranitidine at 9 p.m. on the day before surgery and again the next morning. All patients were anesthetized by well-trained anesthesiologists certified as instructors by the Japanese Society of Anesthesiologists. For induction of anesthesia, thiopental or propofol was used. Vecuronium or succinylcholine was used for endotracheal intubation when the patients were intubated for general anesthesia. Epidural or subarachnoid blockade, if necessary, was performed before induction of general anesthesia. No muscle relaxant was used for the patients who were undergoing orthopedic procedures without blockade. Inhalational anesthesia was performed in mastectomy and orthopedic procedures without blockade. Inhalational anesthesia with epidural blockade was performed in abdominal procedures and LAP-C. Inhalational anesthesia was occasionally applied with subarachnoid blockade or epidural blockade, or for orthopedic procedures with blockade. An intravenous sedative drug was occasionally given supplementally for subarachnoid blockade or epidural blockade in TUR.

Heart rate and blood pressure were retrieved from a series of anesthetic records: (1) upon arrival at the operating room (HR1); (2) immediately after induction of anesthesia (induction of anesthesia was defined as the start of inhalation of anesthesia with a mask or the initiation of neuroaxial blockade, which even was applicable; HR2); (3) immediately after incision (HR3); (4) at the end of the procedure (HR4); and (5) at the end of anesthesia (HR5).

The frequency of atropine injections, the total dose of atropine, and the time intervals between the induction of anesthesia and the injection of atropine were checked from the anesthetic records. Heart rate was noted for the time when each treatment was performed.

To summarize heart rate changes during the operation, one of the following summary scores was chosen after the patient's records were reviewed: 1, no bradycardia occurrence; 2, transient bradycardia without treatment; 3, sustained bradycardia lasting more than 15 min without treatment; 4, sustained bradycardia lasting more than 15 min treated by administration of atropine; 5, severe bradycardia treated by immediate atropine injection; 6, none of the above. When the summary scores were analyzed, score 6 was excluded from the analysis.

The following were studied as potential risk factors for perioperative bradycardia: weight; height; sex; preoperative existence of arrhythmia; hypertension treated with a calcium channel blocker, β blocker, or digitalis; premedication with or without intramuscular atropine or meperidine; drugs used for the induction and maintenance of anesthesia; certain types of inhalational anesthesia; application of endotracheal intubation in patients with general anesthesia; and whether or not epidural or subarachnoid blockade was performed.

Statistical analysis

Demographic data values are presented as means ± SD for continuous variables (e.g., age, weight, and height) and as frequencies and percentages for discrete variables (sex, procedures, etc.). The heart rates at the five observation points are expressed as means ± SD. Differences among the heart rates were analyzed by paired *t*-test with Bonferroni's correction. The heart rates at the time of atropine injection during the operation and the total dose of atropine are expressed as medians and ranges. The time intervals between the induction of the anesthesia and intraoperative atropine injection are expressed as either means ± SD or medians and ranges, according to the dispersion of the obtained data.

Logistic regression was used for each of the five observation points to determine the characteristics involved in the risk of bradycardia. The same analyses were performed to determine any associations between the patient characteristics, on the one hand and, on the other, the frequency of intraoperative atropine injection and the summary scores. For these analyses, simple logistic regressions were used to assess the univariate association of each possible prominent factor with intraoperative bradycardia (HR < 60). The heart rates at five points, the frequency of intraoperative atropine injection, and the summary scores were determined as dependent factors, and the possible prominent factors for bradycardia were determined as independent factors. Separate analyses were performed at each observation point, as well as for the frequency of intraoperative atropine and the summary scores. Variables that achieved a P value of less than 0.05 on univariate analysis were retained for multivariate analysis.

For multivariate logistic regression models, multiple logistic regressions with stepwise backward elimination

of nonsignificant variables were used to identify a set of independent predictors of bradycardia.

The computer software used for these analyses was SPSS 11.0J for Windows (SPSS Japan, Tokyo, Japan).

Results

General profiles of this study

The number of patients (n) and the duration (mean ± SD) of each surgical procedure were as follows: mastectomy ($n = 57$; 138 ± 42 min), abdominal procedures ($n = 114$; 281 ± 132 min), TUR ($n = 77$; 57 ± 31 min), LAP-C ($n = 29$; 92 ± 42 min), orthopedic procedures with blockade ($n = 41$; 104 ± 82 min), and orthopedic procedures without regional blockade ($n = 181$, 132 ± 76 min).

The mean heart rates at each observation point were 77 ± 16 $\cdot$ min^{-1}, 75 ± 15 $\cdot$ min^{-1}, 69 ± 15 $\cdot$ min^{-1}, 71 ± 15 $\cdot$ min^{-1}, and 75 ± 13 $\cdot$ min^{-1} (mean ± SD) upon arrival in the operating room (HR1), after the induction of the anesthesia (HR2), after the surgical incision (HR3), at the end of the operation (HR4), and at the end of anesthesia (HR5), respectively. There were significant differences ($P < 0.001$) between the values at all measured points in all cases, except that between HR2 and HR5 ($P = 0.488$) and that between HR3 and HR4 ($P = 0.035$), when the paired t-test with Bonferroni's correction was used.

The effect of atropine premedication on intraoperative bradycardia, intraoperative atropine usage, and summary scores

Atropine premedication was a significant prominent factor in all three multivariate analyses (intraoperative bradycardia, intraoperative atropine injection, summary scores); (Table 1). Odd ratios (ORs) for bradycardia in patients without atropine versus those with atropine were 2.8, 4.41, 5.51, and 1.86 at HR 1, 2, 3, and 4, respectively. When the patients were divided into two groups according to whether atropine was included in the premedication ($n = 242$) or not ($n = 257$), it was found that 30 patients (11.7%) without atropine premedication were injected intraoperatively with atropine, compared to 3 patients (1.2%) with atropine premedication. In these patients, the goal of using atropine was considered to be the treatment of bradycardia. The time interval between the induction of anesthesia and intraoperative atropine injection was 38.6 ± 31.5 min (mean ± SD; median, 35 min, range, 1–139 min) in patients without atropine premedication, while the intervals in the three patients with atropine premedication were 52, 180, and 250 min. The heart rates at the time of atropine injection during the operation were below 50 $\cdot$ min^{-1} (44 $\cdot$ min^{-1}, 35–50 $\cdot$ min^{-1}; median, range). The frequency of injection was mostly once (once, $n = 28$; twice, $n = 5$). The total doses of atropine injections were 0.2 to 1.0 mg (median, 0.5 mg).

Although the median summary scores in both the atropine premedication group and the no-atropine premedication group were 1, multivariate analysis showed a significant association of no atropine premedication and high summary scores, which indicated a greater likelihood of bradycardia during operation (Table 1).

Other prominent factors, identified by univariate and multivariate analyses, associated with intraoperative bradycardia, intraoperative atropine injection, or summary scores

Intraoperative atropine injection was associated with advanced age and high weight on multivariate analysis (Table 1). Males were more likely than females to experience bradycardia, with a heart rate of less than 60 $\cdot$ min^{-1} upon arrival in the operating room (HR1) and at the end of anesthesia (HR5) in the univariate analysis. In the multivariate analysis, male patients were significantly more likely to have bradycardia, and the OR was 2.93 at HR1 (Table 1).

There were significant differences in the incidence of bradycardia among surgical procedures at HR3, HR4, and HR5 in the univariate study. In the multivariate analysis, surgical procedures were associated with bradycardia at HR5 (Table 1). ORs for bradycardia in Lap-C, TUR, abdominal procedures, and orthopedic procedures with blockades were 7.41, 5.49, 2.89, and 2.68 versus mastectomy, while the OR for orthopedic procedures without blockade was 1.18.

In the multivariate study, bradycardia at HR4 (OR, 3), and the high summary scores, was attributed to propofol used for induction (Table 1).

The multivariate study showed that the absence of endotracheal intubation was a significant risk factor for bradycardia at HR2 (OR, 2.27). Only in the univariate study, bradycardia was significantly induced in the patients with intubation at HR3 and HR4 (Table 1).

Vecuronium, although it fell short of statistical significance ($P = 0.06$) as a risk for bradycardia in the univariate analysis, was included in the multivariate analysis. At HR4, bradycardia was attributed to vecuronium used during anesthesia (OR, 1.71) (Table 1).

Other factors identified by the univariate study, but not significant in the multivariate study

Factors shown to be significantly associated with bradycardia only in the univariate analysis were patient

Table 1. Univariate and multivariate analyses of possible prominent risk factors for bradycardia

Factors (units or percentages of number of patients)	Mean ± SD	*P*					Intraoperative atropine injection	Summary scores
		HR1	HR2	HR3	HR4	HR5	*P*	*P*
Age (years)	56 ± 17	NS	NS	NS	NS	NS	**≤0.05**	NS
Weight (kg)	58.5 ± 11.2	**<0.05**	NS	NS	NS	NS	**≤0.05**	NS
Height (cm)	159.4 ± 9.1	**<0.01**	NS	NS	NS	**<0.01**	NS	NS
Sex (male, 54.3%)		**≤0.01**	NS	NS	NS	**<0.05**	NS	NS
Preoperative calcium channel blocker (10.2%)		NS	NS	NS	NS	NS	**<0.05**	NS
Premedication								
Atropine (48.5%)		**≤0.05**	**≤0.01**	**≤0.01**	**≤0.01**	NS	**≤0.01**	**≤0.01**
Meperidine (89.6%)		NS	NS	NS	NS	NS	NS	NS
Procedures with blockade (52.2%)		NS	NS	**<0.05**	**<0.01**	**≤0.01**	NS	NS
Induction agent (propofol, 66.3%; thiopental, 24.2%)		NS	NS	NS	**≤0.01**	**<0.01**	NS	**≤0.05**
Muscle relaxant for induction (vecuronium, 34.5%; succinylcholine, 16.2%)		NS	NS	NS	NS	NS	NS	NS
Endotracheal intubation (54.7%)		NS	**≤0.01***	**<0.05****	**<0.05****	NS	NS	NS
Maintenance of anesthesia								
N2O (67.5%)		NS	NS	**<0.05**	**<0.05**	**<0.05**	NS	NS
Fentanyl (30.1%)		NS	NS	**<0.05**	NS	NS	NS	NS
Propofol (14.6%)		NS	NS	NS	NS	**<0.05**	NS	NS
Vecuronium (27.1%)		NS	NS	NS	**0.06**	NS	NS	NS
Intraoperative ephedrine (13.6%)		NS	NS	NS	NS	NS	NS	NS
SAB (22%)		NS	NS	NS	NS	**<0.01**	NS	NS
EDB (38.3%)		NS	**<0.05**	NS	NS	**<0.01**	NS	NS

*Bradycardia was significantly induced in the patients without intubation at HR2; **Bradycardia was significantly (only in univariate study) induced in the patients with intubation at HR3 and HR4

The heart rates at five points, the frequency of intraoperative atropine injection, and the summary scores were determined as dependent factors, and the possible prominent risk factors for bradycardia were determined as independent factors. Separate analyses were performed at each observation point, as well as for the frequency of intraoperative atropine and the summary scores. Variables that achieved a *P* value of less than 0.05 on univariate analysis were retained for multivariate analysis. Bold figures show significance on univariate analysis, except for vecuronium for maintenance of anesthesia. Underlined figures show significance on multivariate analysis. Summary scores: 1, no bradycardia occurrence; 2, transient bradycardia without treatment; 3, sustained bradycardia lasting more than 15 min without treatment; 4, sustained bradycardia lasting more than 15 min treated by administration of atropine; 5, severe bradycardia treated by immediate atropine injection; 6, none of the above. Score 6 was excluded from the analysis

SAB, subarachnoid blockade; EDB, epidural blockade; NS, not significant

height, the use of a preoperative calcium channel blocker, the use of nitrous oxide, the use of fentanyl and propofol to maintain anesthesia, and the use of epidural or subarachnoid blockade. These factors failed to be significant in the multivariate analysis (Table 1).

Discussion

Our study demonstrated that the most prominent risk factor for bradycardia during anesthesia was the absence of atropine premedication; interestingly, this affected most of the designated measured points, from arrival in the operating room until the end of the operation. This effect was also manifested in the frequency of the usage of intraoperative atropine, and the summary scores indicating the frequency of the appearance of bradycardia. Therefore, atropine premedication attenuated the incidence of bradycardia during the entire period of the operation, even though it was given only once, in the patients' ward. Many earlier studies have already shown the effectiveness of atropine pretreatment to prevent bradycardia during spinal anesthesia [6] or epidural anesthesia [7]. These reports also support the long action of atropine pretreatment during surgery. Lesser et al. [8] reported the risk of intraoperative bradycardia to be 10.2%, but they indicated that low baseline heart rates and male sex contributed even more to the incidence of bradycardia during anesthesia. Atropine premedication is becoming controversial [9], and atropine is seldom given as premedication in anesthetic practice in the United States and the United Kingdom [9] (except to infants who tend to exhibit bradycardia during the induction of anesthesia [10]). Albeit there is a major trend toward atropine disuse, atropine

pretreatment may be worthwhile to be reevaluated, because its prophylactic effect did last for the entire period of the surgical operation. Sudden bradycardia is often induced by an abrupt vagal reflex during endotracheal intubation and the strong retraction of splanchnic organs, and this sudden bradycardia could be avoided by atropine pretreatment [11].

Neuroaxial blockade has been suspected to have a strong impact on heart rate. Carpenter et al. [12] reported that 13% of patients in whom spinal or epidural anesthesia was used had bradycardia. We found that surgical procedures with neuroaxial blockade—Lap-C, TUR, and both abdominal and orthopedic procedures with blockade—showed higher odds ratios for the incidence of bradycardia (odds ratio, 2.6–7.4). Interestingly, the blockade's effect on heart rate became most apparent after anesthesia ended, being shown only in the univariate study. Therefore, blockade-induced bradycardia is likely to be concealed by other factors during operation.

Because meperidine has an anticholinergic action, it could be a confounding factor. However, it did not show any relationship with bradycardia throughout the procedures (Table 1). Vecuronium is known to induce bradycardia [13–15]. There was a report of cardiac arrest following vecuronium injection associated with abdominal retraction in a patient without atropine premedication. In the present study, this effect was seen only after the operations had ended. Surgical stimulation may have overcome the effect of vecuronium. This factor, vecuronium, was also likely abolished by other factors.

Other factors affecting heart rate were sex, propofol induction, endotracheal intubation, and nitrous oxide. Bradycardia was more likely to occur in males than in females upon their arrival in the operating room. This sex difference was abolished after anesthesia was induced. The sole sex effect seems to be weak and is likely to be dominated by other factors, such as subsequent blockade and endotracheal intubation. Endotracheal intubation increased heart rate, as expected, but this increase did not last long. The factors affecting heart rate keep changing throughout the period of anesthesia. It was hard to find a comprehensive reason for the positive effect of induction agents on heart rate at HR4 and HR5. Because propofol reduces the heart rate more than thiopental, it is feasibile that an initial potential factor affecting heart rate would exert its influence throughout the anesthesia period.

In our study, atropine was injected only once in most patients, and the total doses of the injections were around 0.5 mg. Thus, bradycardia in this study was alleviated promptly after the injection of atropine. However, close observation is necessary in patients with cardiac dysfunction, in whom severe bradycardia may lead to low cardiac output and hence to coronary ischemic changes.

The data were retrospectively extracted from the anesthesia records and therefore we may have failed to identify transient bradycardia. Also the sampling time points were fixed, and transient bradycardia may have been missed for this reason. Since the data sample was large (499 patients), we consider that the overall tendency would not have been influenced by such transient events. We think that there might be a bias in regard to the usage of intraoperative atropine in our study, because the anesthetists were aware of atropine premedication. Another shortcoming of this study was that we investigated limited surgical procedures and the patients were ASA physical status 1 and 2. Further studies including patients with cardiac complications are necessary to confirm the effect of atropine premedication and other factors on heart rate during surgeries.

In conclusion, the most prominent factor to affect heart rate was atropine premedication. An unexpectedly noteworthy finding was that a single preoperative administration of atropine affected the heart rate throughout the operation, whereas other factors, such as the use of muscle relaxants, endotracheal intubation, and blockade, each affected heart rate only temporarily.

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