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Original Article

Factors associated with transient bradycardia during local anesthesia administration to the oral cavity under intravenous sedation: A retrospective cohort study

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KEYWORDS
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Abstract *Background/purpose:* The possibility of triggering the trigeminocardiac reflex (TCR) during oral surgery is considerably lower than that during other surgeries. A reduced heart rate (HR) of ≥20% from baseline is usually considered a diagnostical criterion for the TCR. Our automated anesthesia charting system often revealed cases of slight transient HR decrease during sedation. We aimed to explore its incidence and associated factors during local anesthesia administration under intravenous sedation.
Materials and methods: This study analyzed the data of 2636 cases that received infiltration anesthesia under intravenous sedation from 2008 to 2010 and had vital signs recorded using an automated anesthesia charting system. Especially, data concerning the average HR before anesthesia and the minimum HR between the initiation and end of anesthesia from anesthetic records were extracted. Moreover, data regarding patients' medical history and unusual reactions during dental treatment were collected. Multivariate logistic regression analysis was performed to identify factors associated with transient bradycardia (TB).
Results: TB occurred in 472 patients (17.9%); no patient developed hypotension or any associated symptoms, suggesting that intravenous sedation was effective in stabilizing vital signs. The factors associated with TB were younger age, gag reflex, and allergy to local anesthetics. There were no differences in sex, patient history, or dose of sedatives between patients with TB and those without TB.

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Conclusion: The incidence of TB during infiltration anesthesia under sedation was found to be higher than that previously reported. Additionally, young age and gag reflex were identified as factors associated with bradycardia development.

Introduction

Administering local anesthesia in the oral cavity causes occasional transient decreases in the heart rate (HR) and blood pressure (BP). Syncope or presyncope frequency during dental surgery under intravenous sedation is approximately 0.85%, and hypotension frequency during local dental anesthesia is approximately 0.08%.[1,2] These phenomena may result from the trigeminocardiac reflex (TCR) triggered by nociceptive stimulation of the maxillary and mandibular nerves or the vasovagal reflex (VVR) triggered by emotional stress and nociception.[3—5] Sedation in patients with a history of hypotensive reactions to local anesthesia can prevent such reactions during procedures, suggesting that emotional stress triggering the VVR is the main cause of bradycardia and hypotension associated with local anesthesia.[6] TCR triggering can also lead to syncope during dental treatment (i.e., factors other than emotion may contribute to its development).[7] However, the possibility of triggering the TCR during oral surgery is estimated to be 1—2%, significantly lower than that caused by ophthalmic (25—90%) and skull base (8—18%) surgeries performed under general anesthesia.[8,9] The reasons for this difference have not been thoroughly investigated. Most previous studies on the TCR have used a reduced HR of ≥20% from baseline as a criterion, but this criterion might underestimate the incidence of TCR triggering.[10,11]

Sustained bradycardia and consequent hypotension are rarely observed during oral surgery under intravenous sedation; mild transient bradycardia (TB), most likely due to local anesthesia or abrupt surgical invasion, occurs occasionally but recovers quickly. Furthermore, sedation during dental treatment can prevent subjective symptoms caused by this transient change. Few detailed studies on such TB cases have been performed recently.[12] An automatic anesthesia recording system is used in our dental anesthesia clinic. We reviewed the data regarding changes in HR and observed cases of transient and mild 5—10-bpm HR decreases during local anesthesia administration, many of which might have been missed previously. Analyzing this finding could provide new knowledge regarding TCR triggering during dental treatment. We hypothesized that the TCR due to stimulation of the oral cavity is not less common than that in other trigeminal innervated areas. Therefore, this study aimed to investigate the incidence and etiology of bradycardia after local anesthesia administration in the oral cavity through a retrospective analysis of treated cases.

Materials and methods

This observational study examined TB occurrence after administration of infiltration anesthesia in patients under intravenous sedation between April 1, 2008, and March 31, 2010, at a dental anesthesiology clinic. The ethics committee of our university (No. D2021-001) approved the study procedures. The study was conducted in accordance with the tenets of the Helsinki Declaration. In accordance with our university's Ethical Guidelines for Medical and Health Research Involving Human Subjects, the study contents were disclosed and posted on the hospital's website instead of obtaining individual written consent.

TB was diagnosed according to the following protocols, and the data were automatically extracted from the anesthesia records (paperChart; https://paperchart.net/ech/). HR was recorded at 2-s intervals throughout anesthesia management. The HR at the start of local anesthesia (HRLA) was the average HR measured 5 min before administering infiltration anesthesia and was calculated using the recorded HR data. HRMin was defined as the minimum HR measured 0—5 min after administering infiltration anesthesia, and the HR ratio of variation (HRR) was calculated based on each type of HR as follows:

$$HRR\ (\%) = ([HRMin] - [HRLA])/[HRLA] \times 100$$

A decrease in HRR of <10% was defined as TB based on previous reports that showed a 10—20% HR decrease by TCR triggering.[11,13] Clinical data including age, sex, height, weight, dosage of sedatives used, systemic diseases, and reasons for using sedation (e.g., dental phobia, gag reflex, allergy to drugs [excluding local anesthesia], discomfort during local anesthesia, hyperventilation, allergy to local anesthetics, VVR, and large invasion) were collected. The treating dentist determined the reasons, and multiple choices were allowed. The term "large invasion" was chosen when the dental procedure was expected to be more invasive or time-consuming than usual. Dental phobia was assigned when the patient requested sedation due to fear of conscious treatment. Local anesthetic allergy was treated separately from other drug allergies to consider potential adverse reactions during local anesthesia.

The patients were divided into two groups: those with observed TB (TB group) and those without observed TB (Normal group). SPSS 28.0 software (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Categorical variables were compared between the groups using either the chi-squared test or two-sided Fisher's exact test, while continuous variables were compared using the independent-samples *t*-test. A binary logistic regression model was employed to identify risk factors for TB during local anesthesia. A two-tailed *P*-value of <0.05 indicated statistical significance.

Results

A total of 2673 patients were initially included; however, 37 were excluded due to missing data on sex, height, or

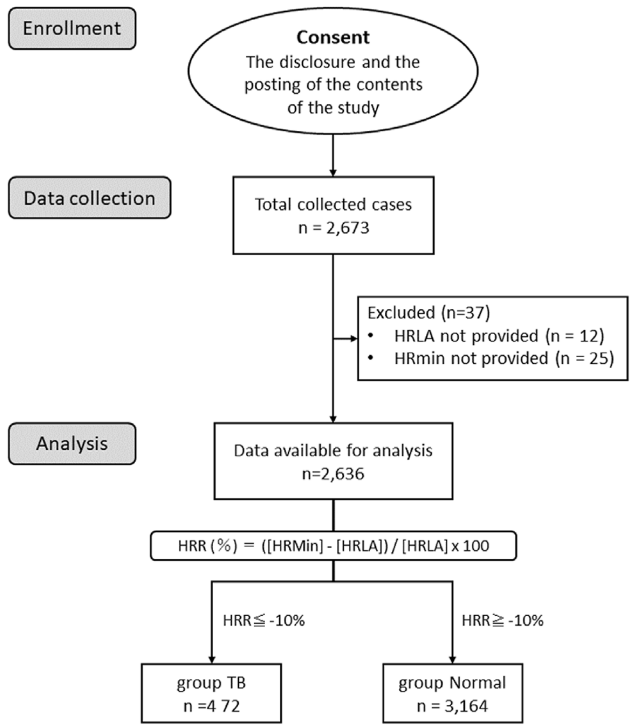

Figure 1 Flowchart of data collection.
The included patients were classified into groups with and without observed transient bradycardia (TB). The occurrence of TB was determined based on the heart rate ratio of variation (HRR).
HRLA, heart rate at the start of local anesthesia; HRmin, minimum heart rate 0–5 min after administrating local anesthesia.

weight, leaving 2636 patients for analysis. TB was evident in 472 of the 2636 patients (17.9%; Fig. 1). There was no incidence of severe hypotension leading to a loss of consciousness, and no medication or treatment was administered. Table 1 shows the demographic and pharmacologic data of the patients. No significant differences were observed in sex, height, or weight between the two groups. In our hospital, midazolam (MDZ) 0.02–0.05 mg/kg and propofol 0.2–0.5 mg/kg are administered initially, followed by propofol 1–3 mg/kg/h, to maintain a Richmond Agitation Sedation Scale score of 3 (movement or eye-opening to voice, but no eye contact). The mean MDZ dose was significantly higher in the TB group than in the Normal group, but the mean propofol dose did not differ significantly between the groups.

The age distribution differed significantly between the TB and Normal groups (Table 2). To further compare the age distribution of the groups, patients were divided into four subgroups by fractions of 20 years (Table 2). There was a significant difference in patient age between the TB and Normal groups. TB was more common in patients aged 20–39 years than in those aged ≥40 years. The TB group had a significantly higher number of patients with dental phobia, gag reflex, and allergy to local anesthetics but a significantly lower number of patients with large invasions than the Normal group.

Table 3 shows the results of the univariate and multiple logistic regression model using the forced-entry method. Patient age of 20–39 years (odds ratio [OR], 1.704; 95% confidence interval [CI], 1.255–2.315; $P = 0.001$), gag reflex (OR, 1.572; 95% CI, 1.068–2.315; $P = 0.022$), and allergy to local anesthetics (OR, 6.152; 95% CI, 2.334–16.221; $P < 0.001$) were significantly associated with TB likelihood (Table 3). However, no systemic disease was found to be associated with TB.

Discussion

In this study, we retrospectively analyzed 2636 patients under intravenous sedation, mainly those undergoing minor oral surgeries with a fear of dental treatments. To our knowledge, this study is the first to investigate HR changes induced by a mild stimulus of local anesthesia in the orofacial region in sedated patients. A systolic BP < 60 mmHg was defined as hypotension.[14,15] The results showed that all patients could be safely treated without developing syncope due to hypotension induced by bradycardia, and intravenous sedation was effective in stabilizing the vital signs of patients. Bradycardia, which often causes syncope during local anesthesia, is caused by the VVR, triggered by psychological stress from anxiety and fear of dental treatment. Intravenous sedation has been reported to suppress this reflex,[6,16] which is supported by our study findings. Another possible cause of bradycardia is the TCR triggered when the trigeminal-dominant area is stimulated. It occurs independent of psychological stress and has a low incidence during maxillofacial surgery, despite unclear causation.[8,9] In the ocular reflex, which is a TCR type, the intensity and duration of the stimulation are associated with the degree of

Table 1 Demographic and pharmacologic characteristics of patients with transient bradycardia (TB).

Variables	TB (n = 472)		Normal (n = 2164)		p-value
	mean	SD	mean	SD	
Height (cm)	160.91	8.38	161.33	8.84	0.331
Weight (kg)	57.13	11.42	57.86	11.74	0.214
Average propofol dosage (mg/kg/h)	1.44	1.19	1.36	1.20	0.188
Average midazolam dosage (mg/kg/h)	0.048	0.033	0.042	0.031	0.002

SD, standard deviation.

Table 2 Age distribution and clinical characteristics of patients with transient bradycardia (TB)

Variables	TB (n = 472)		Normal (n = 2164)		p-value
	n	Presence (%)	n	Presence (%)	
Age (years)					
0–19	13	2.8	32	1.5	0.074
20–39	164	34.8	472	21.8	<0.001
40–59	144	30.5	857	39.6	<0.001
≥60	151	32.0	803	37.1	0.039
Sex (female)	311	65.89	1357	62.71	0.206
Large invasion	215	45.6	1117	51.6	0.017
Dental phobia	209	44.3	810	37.4	0.006
Hypertension	62	13.1	356	16.5	0.074
Diabetes	22	4.7	140	6.5	0.138
Psychologic diseases	32	6.8	111	5.1	0.152
Respiratory diseases	23	4.9	86	4.0	0.372
Arrhythmias	20	4.2	71	3.3	0.302
Neurological diseases	14	3.0	74	3.4	0.619
Hyperlipidemia	10	2.1	52	2.4	0.867
Liver diseases	8	1.7	49	2.3	0.599
Ischemic heart diseases	7	1.5	32	1.5	1.000
Heart diseases	7	1.5	31	1.4	0.834
Gastrointestinal diseases	2	0.4	32	1.5	0.072
Musculoskeletal diseases	3	0.6	26	1.2	0.462
Urinary diseases	1	0.2	25	1.2	0.070
Connective tissue diseases	4	0.8	18	0.8	0.973
Hyperthyroidism	3	0.6	24	1.1	0.248
Hypothyroidism	5	1.1	11	0.5	0.248
Gag reflex	47	10.0	132	6.1	0.003
Allergy for drugs	14	3.0	53	2.4	0.518
Phobia	8	1.7	24	1.1	0.350
Discomfort during local anesthesia	5	1.1	17	0.8	0.575
Hyperventilation	5	1.1	16	0.7	0.565
Allergy for local anesthetics	11	2.3	8	0.4	<0.001
Vasovagal response	2	0.4	4	0.2	0.293

Values are presented as number and %.

symptoms; therefore, the same trend can be assumed to occur in the maxillofacial region.[17,18] The results revealed that only mild bradycardia without syncope due to hypotension was observed after administering local anesthesia in the maxillofacial region because the stimulus from needle puncture is much weaker and more momentary than the ocular reflex.[7] Additionally, as these cases of bradycardia occurred during sedation, they could be caused by the TCR; thus, the incidence of the reflex would be comparable to that observed during otolaryngological or skull base surgery, which explains the low incidence in maxillofacial surgery.[9,10] Furthermore, experienced surgeons can administer anesthesia in a less invasive manner. In our clinic, a board-certified oral surgeon or an individual who is recognized within the facility as an equivalent performs treatments under sedation. Therefore, their local anesthetic technique is considered less invasive. Meanwhile, because pain points are more common in the anterior teeth and less common in the molars, the difference in pain by injection site may be related to the occurrence of TB. The injection site could not be investigated in this study. Moreover, the local anesthetic dose was not investigated because TB is caused by pain stimuli immediately after penetration; therefore, the influence of the local anesthetic dose used after penetration is considered negligible.

In contrast, this study collected data in a retrospective manner with a definition of TB of >10%. Thus, the possibility of including false-positive cases remains. The criterion of a decrease in HR variability of ≤20% might underestimate the true TCR incidence.[19] However, the present study was inspired by the clinical question of what causes the mild HR decrease (5–10 bpm) that is often observed during local anesthesia, with a 1–2-min recovery time based on observations in the electronic anesthesia records. By including the cases of 10–20% HR decrease that were previously ignored because of potential false positives, the present study aimed to clarify TB incidence and identify possible unknown background triggers underlying these cases. Future prospective studies should be conducted to determine the true positives.

Preoperative mental tension may enhance TCR triggering; particularly, the VVR and TCR can induce syncope

Table 3 Binary logistic regression analysis of variables on patients with transient bradycardia (TB).

	Univariate analysis					Multivariate analysis				
	OR	95% CI			p-value	OR	95% CI			p-value
Age (years)										
≥60	1					1				
0—19	2.160	1.108	—	4.212	0.024	2.003	0.995	—	4.031	0.052
20—39	1.848	1.441	—	2.369	<0.001	1.704	1.255	—	2.314	0.001
40—59	0.894	0.697	—	1.145	0.373	0.865	0.661	—	1.132	0.290
Sex (Female)	1.149	0.932	—	1.416	0.194	1.082	0.789	—	1.484	0.626
Height	0.995	0.983	—	1.006	0.347	0.990	0.972	—	1.008	0.265
Weight	0.995	0.986	—	1.003	0.221	1.004	0.992	—	1.016	0.523
Average propofol dosage (mg/kg/h)	1.055	0.973	—	1.144	0.192	0.990	0.900	—	1.089	0.838
Average midazolam dosage (mg/kg/h)	108.272	5.807	—	2018.618	0.002	7.673	0.239	—	246.375	0.250
Large invasion	0.784	0.642	—	0.958	0.017	0.952	0.753	—	1.205	0.684
Dental phobia	1.300	1.062	—	1.592	0.011	1.139	0.907	—	1.431	0.264
Hypertension	0.768	0.575	—	1.027	0.075	0.943	0.676	—	1.315	0.730
Diabetes	0.707	0.446	—	1.121	0.140	0.882	0.541	—	1.440	0.616
Psychologic diseases	1.345	0.896	—	2.020	0.153	1.073	0.689	—	1.669	0.756
Respiratory diseases	1.238	0.773	—	1.983	0.375	1.018	0.613	—	1.689	0.946
Arrhythmias	1.304	0.786	—	2.165	0.304	1.299	0.751	—	2.246	0.349
Neurological diseases	0.863	0.483	—	1.542	0.620	0.858	0.465	—	1.581	0.623
Hyperlipidemia	0.879	0.444	—	1.743	0.712	1.035	0.507	—	2.116	0.924
Liver diseases	0.744	0.350	—	1.582	0.443	0.881	0.407	—	1.910	0.749
Ischemic heart diseases	1.003	0.440	—	2.286	0.994	1.272	0.543	—	2.976	0.580
Heart diseases	1.036	0.453	—	2.367	0.934	0.928	0.385	—	2.239	0.868
Gastrointestinal diseases	0.284	0.068	—	1.187	0.084	0.345	0.081	—	1.464	0.149
Musculoskeletal diseases	0.526	0.159	—	1.745	0.294	0.606	0.174	—	2.104	0.430
Urinary diseases	0.182	0.025	—	1.344	0.095	0.252	0.034	—	1.894	0.181
Connective tissue diseases	1.019	0.343	—	3.025	0.973	1.075	0.347	—	3.330	0.900
Hyperthyroidism	1.744	0.523	—	5.814	0.366	1.424	0.420	—	4.832	0.571
Hypothyroidism	3.636	0.735	—	18.000	0.114	3.546	0.697	—	18.054	0.127
Gag reflex	1.702	1.201	—	2.413	0.003	1.572	1.068	—	2.315	0.022
Allergy for drugs	1.218	0.670	—	2.213	0.519	0.923	0.479	—	1.779	0.811
Phobia	1.537	0.686	—	3.443	0.296	1.341	0.578	—	3.110	0.494
Discomfort during local anesthesia	1.352	0.496	—	3.683	0.555	1.058	0.369	—	3.028	0.917
Hyperventilation	1.437	0.524	—	3.943	0.481	0.901	0.311	—	2.613	0.848
Allergy for local anesthetics	6.431	2.572	—	16.076	<0.001	6.152	2.334	—	16.221	<0.001
Vasovagal response	2.298	0.420	—	12.582	0.338	1.869	0.332	—	10.536	0.478

CI, confidence interval; OR, odds ratio.

after local anesthesia administration. Dental fear causes overstimulation of the parasympathetic and sympathetic nervous systems.[20,21] During consciousness, mild bradycardia caused by the TCR disrupts the delicate balance in the autonomic nervous system, resulting in severe bradycardia and syncope. However, as the autonomic nervous system is not hyperexcited during sedation, the balance is not disturbed. Therefore, syncope does not occur, and only mild bradycardia may be observed, as demonstrated herein. Another possibility is that the VVR was triggered, but only bradycardia occurred without hypotension or with only mild hypotension. In any case, sedation suppresses local anesthesia-induced syncope, although further prospective studies are required to determine the incidence of TB and its associated factor, in addition to whether this bradycardia is caused by TCR, VVR, or both.

This was an exploratory study to examine factors associated with TB; all factors obtained were used as independent variables. Logistic regression analysis revealed that gag reflex and patient age of 20—39 years were independent factors associated with TB development. In patients with an exaggerated vomiting reflex, the vomiting center may be hyperactivated by afferent stimulation via the glossopharyngeal nerve, and the parasympathetic nervous system may be stimulated efferently.[22,23] In the VVR, where the parasympathetic nervous system is stimulated by various causes, the vomiting reflex is triggered, and nausea may occur.[22,24] Additionally, swallowing and coughing are known to cause situational syncope. Although the causal relationship between nausea/vomiting and bradycardia is unclear, patients with a known history of nausea/vomiting may easily develop parasympathetic hyperactivity, leading to bradycardia. Patients aged 20—39 years were more likely to develop TB. A similar trend was also observed in patients aged <20 years ($P = 0.052$; OR, 2.003; 95% CI, 0.995—4.031). In this study, as the incidence according to age was not the primary objective; further, because the number of independent variables would increase with a 10-year age division, the age categories were broadly divided as follows: under puberty (0—19 years), young adults (20—39 years), middle-aged adults (40—59 years), and older adults (≥60 years). Younger people have higher parasympathetic sensitivity and are at a higher risk of triggering the VVR.[18,25,26] These factors may be related to parasympathetic hyperactivity inducing the VVR and potentially to the TCR, although the details remain unknown.

The adjusted OR for allergy to local anesthetics was much higher than that for other factors. However, the frequency of actual allergy to local anesthetics is very low, and many abnormal reactions associated with local anesthesia are caused by different factors.[27,28] Therefore, cases classified as exhibiting an allergy to local anesthetics could actually have been cases of (pre)syncope due to local anesthesia, having been classified by a non-specialist dentist.[29] In the univariate analysis, the mean MDZ dosage and the number of patients with dental phobia and with large invasion were higher in the TB group; in contrast, these factors were not found to be significant risk factors for TB in the multivariate analysis. This may be because the term "dental phobia" or "large invasion" is often used for patients who have experienced discomfort during dental treatment in the past or who simply want to be treated under sedation for convenience. Sedation may also cause bradycardia, whereas MDZ has a limited effect on parasympathetic tone and does not cause bradycardia.[30] These factors may not be independent risk factors for TB because patients with dental phobia require higher doses of MDZ for their nervousness.

This study had some limitations. First, it was a preliminary study, and the HR extraction method employed might have included decreases in HR caused by the VVR and other factors, such as sedation and false recording due to body movements. Second, as a retrospective observational study, it used all data collected, but the sample size might not have been sufficient to draw definitive conclusions. However, the findings might remain consistent, even with an increased sample size, for the parameter that was found to have a difference in this study. In addition, owing to the limited sample size, differences might be falsely considered nonsignificant, potentially affecting other factors assessed to show no difference. Therefore, obtaining a larger sample size might provide additional support for the parameters that demonstrated differences in this study. To improve the credibility of the results, a prospective study should be conducted under the following conditions: (1) sample size determination based on the hypothesis that certain factors are associated with bradycardia, (2) detailed evaluation of patients' discomfort during dental treatment, (3) maintenance of sedation depth to prevent VVR, and (4) identification of TB through real-time observation of HR changes. Future investigations conducted under these conditions would advance the understanding of the relationship between dental procedures and bradycardia, thereby yielding more reliable and comprehensive results.

In conclusion, this study found that TB caused by local anesthesia occurred more frequently than previously reported, and younger age and gag reflex, which are related to parasympathetic hyperactivity, were associated with decreased HR after regional anesthesia. Despite the clear association between TCR and TB, there remains controversy concerning whether all TB cases in this study resulted solely from TCR due to infiltration anesthesia. Further research is required to explore and clarify this aspect.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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