Hemodynamic changes in regular antipsychotic users after adrenaline-containing lidocaine injection under general anesthesia: a prospective study

Yoshiki Shionoya (✉ yoshiki@tky.ndu.ac.jp)

Nihon Shika Daigaku Fuzoku Byoin <https://orcid.org/0000-0001-5012-4907>

Eishi Nakamura

Nihon Shika Daigaku Fuzoku Byoin

Gentaro Tsujimoto

Nihon Shika Daigaku Fuzoku Byoin

Takayuki Koyata

Nihon Shika Daigaku Fuzoku Byoin

Asako Yasuda

Nihon Shika Daigaku Fuzoku Byoin

Kiminari Nakamura

Nihon Shika Daigaku Fuzoku Byoin

Katsuhisa Sunada

Nihon Shika Daigaku Fuzoku Byoin

Research article

Keywords: Adrenaline, Antipsychotics, General anesthesia, Interaction, Local anesthesia

Posted Date: March 16th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-17266/v1>

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Abstract

Background: Local anesthetic containing adrenaline is commonly used in many operations to maintain hemostasis and prolong the duration of anesthesia. Antipsychotic drugs have an α -adrenergic receptor blocking action, and it is thought that β -adrenergic receptors predominate when adrenaline is administered in combination, thus inducing hypotension. Many general anesthetics have vasodilatory effects, and it is possible that blood pressure may decrease further if adrenaline-containing lidocaine is administered to antipsychotic users during anesthesia. This study aimed to assess the circulation dynamics in regular antipsychotics users administered adrenaline-containing lidocaine under general anesthesia in a dental procedure.

Methods: Participants included 30 patients regularly using antipsychotics (butyrophenone, phenothiazine, and/or atypical antipsychotics) who were scheduled for dental treatment to be performed under general anesthesia. At five minutes after tracheal intubation, the systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and percutaneous oxygen saturation (SpO₂) were measured as a baseline. SBP, DBP, HR, and SpO₂ were measured 2, 4, 6, 8, and 10 minutes after the injection of 1.8 mL of 2% lidocaine (32 mg) with 1:80,000 adrenaline (22.5 μ g) into the oral cavity. Differences in the SBP, DBP, HR, and SpO₂ between baseline and at each time point were analyzed using Dunnett's test.

Results: No significant changes were observed in the SBP, DBP, HR, and SpO₂ compared to baseline until ten minutes after the administration of adrenaline-containing lidocaine. No adverse events were observed up to one hour after the administration of adrenaline-containing lidocaine.

Conclusions: This study demonstrated that adrenaline used at the usual dose for dental treatment under general anesthesia is unlikely to affect the circulation dynamics of regular antipsychotic users.

Background

Local anesthetic containing epinephrine provides several advantages; increasing the duration of anesthetic effect, decreasing the systemic toxicity of local anesthetics, providing hemostasis at the surgical site, and enhancing the quality of the neural blockade [1–4]. Since antipsychotic drugs have an α -adrenergic receptor blocking action [5], it is thought that when adrenaline is used in combination, β -adrenergic receptors predominate and peripheral blood vessels are dilated, inducing hypotension. Therefore, lidocaine containing adrenaline should be carefully administered in patients who are being treated with antipsychotics, such as patients with schizophrenia, autism, intellectual disability, and dementia. Okada et al. [6] reported a schizophrenic patient with risperidone overdose who experienced unexpected hypotension in response to noradrenaline infusion. They believe that this unexpected hypotension in response to catecholamine infusion was caused by the α -adrenergic blockade effect of risperidone. However, no prospective study has assessed the effects of the interaction between dental adrenaline-containing lidocaine and antipsychotics on circulatory dynamics.

Because of uncooperative nature/poor compliance, general anesthesia is often necessary for the dental treatment of regular antipsychotics users. Since many general anesthetics have vasodilatory effects, it is possible that blood pressure may further decrease if adrenaline-containing lidocaine is administered to antipsychotic users during anesthesia. The purpose of the present study was to clarify the circulation dynamics in regular antipsychotics users administered adrenaline-containing lidocaine under general anesthesia in a dental procedure.

Materials And Methods

This study was approved by the Ethics Committee of The Nippon Dental University School of Life Dentistry Tokyo, Japan (approval number NDU-T-2015-14) and was performed in accordance with their guidelines and the guidelines of the Declaration of Helsinki. It was conducted after clinical trial registration as certified by the International Committee of Medical Journal Editors (trial identification number UMIN000016644). Informed consent was obtained from all individual participants or legal guardians included in the study.

This was a prospective study performed at Nippon Dental University Hospital Tokyo, Japan. Participants included 30 patients regularly using butyrophenone, phenothiazine, and/or atypical antipsychotics for more than three months who were scheduled for dental treatment to be performed under general anesthesia. Patients were excluded from the study if any of the following criteria were met: age < 18 years; age ≥ 65 years; an American Society of Anesthesiologists (ASA) physical status 3 or 4; taking circulatory drugs and/or antidepressants drugs; a history of allergy to lidocaine or any of the other ingredients used in the study; and patients with hypertension, heart failure, diabetes, and hyperthyroidism.

No premedication was administered in any patient. Routine anesthesia monitoring consisted of electrocardiography, pulse oximetry, non-invasive blood pressure, capnography, and Bispectral Index (BIS) monitors. With 100% oxygen administered from a face mask, general anesthesia was induced with propofol and remifentanyl using a syringe pump (TE-332S, Terumo, Tokyo, Japan) after the intravenous line was secured. If or when venous access was difficult to establish, slow induction using sevoflurane was selected and shifted to anesthesia with propofol and remifentanyl after losing consciousness. The administration of remifentanyl was terminated immediately after nasotracheal intubation using rocuronium bromide (0.6 mg/kg), and anesthesia was maintained using propofol so as to BIS values between 40 and 60.

At the point of five minutes after discontinuation of remifentanyl, blood pressure, heart rate, and oxygen saturation were measured as a baseline. Immediately after measuring the baseline, 1.8 mL of 2% lidocaine (32 mg) with 1:80,000 adrenaline (22.5 µg) was administered to the oral cavity via buccal mucosa slowly over 30 seconds with a 30-gauge needle. The systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and percutaneous oxygen saturation (SpO₂) were measured 2, 4, 6, 8, and 10 minutes after completing the administration of adrenaline-containing lidocaine. When the SBP fell below 70 mmHg, the cardiovascular agent was administered, and the administration time, drug name,

and dosage were recorded. From that point, 10 minutes after completing the administration of adrenaline-containing lidocaine, dental treatment was started, remifentanyl administration was resumed, and anesthesia was maintained with oxygen, air, propofol, and remifentanyl. SBP, DBP, HR, and SpO₂ were measured at 5-minute intervals during dental treatment, and adverse events up to one hour after administration of adrenaline-containing lidocaine were examined.

All numerical data are expressed as means $\pm$ standard deviation. Differences in SBP, DBP, HR, and SpO₂ between baseline and at each time point were analyzed using Dunnett's test. All statistical analyses were performed using Statistical Package for Social Sciences Version 24.0 (IBM, Armonk, NY). P values < 0.05 were considered statistically significant.

Results

The study sample consisted of 30 patients. Patient characteristics are presented in Table 1. All patients were ASA 1, and perioperative data are detailed in Table 2. In four cases, slow induction using sevoflurane was selected, and in the other 26 cases, an intravenous line could be secured.

Changes in SBP, DBP, HR, and SpO₂ over time are presented in Figs. 1–3. No significant changes were observed in the SBP, DBP, HR, and SpO₂ until 10 minutes after the administration of adrenaline-containing lidocaine. The systolic blood pressure never dropped below 70 mmHg during general anesthesia, and the cardiovascular agent was not administered. No adverse events were observed up to one hour after the administration of adrenaline-containing lidocaine

Table 1. Patient characteristics		
Patient demographics		
Age (mean $\pm$ SD, years)		24.6 $\pm$ 4.9
Sex (male/female)		26/4
Weight (mean $\pm$ SD, kg)		75.4 $\pm$ 19.2
Height (mean $\pm$ SD, cm)		168.6 $\pm$ 8.3
BMI (mean $\pm$ SD, kg/m ²)		26.5 $\pm$ 5.9
Prescribed Antipsychotics		n (includes overlaps)
Butyrophenones		
Haloperidol		5
Bromperidol		1
Phenothiazine		
Propericiazine		1
Levomepromazine		5
Atypical antipsychotics		
Risperidone		16
Olanzapine		3
Aripiprazole		10
Prescribed reason		n (includes overlaps)
Intellectual disability		20
Autism		16
Schizophrenia		2
Table 2. Patient perioperative data		
Blood concentration of propofol at time of induction (μ g/mL)		3.7 $\pm$ 0.8
Infusion rate of remifentanyl at time of induction (μ g/kg/min)		0.25 $\pm$ 0.06
Rocuronium doses for intubation (mg)		50.7 $\pm$ 9.4
Blood propofol concentration at time of adrenaline-containing lidocaine injection (μ g/mL)		2.7 $\pm$ 0.5
Surgical time (min)		59.8 $\pm$ 33.4

Table 1. Patient characteristics	
Anesthesia time (min)	113.4 ± 36.2
The total dose of propofol (mg)	772.1 ± 339.5
The total dose of remifentanyl (μg)	1083.3 ± 572.2

n = 30; values are presented as mean ± SD.

Discussion

In the present study, we assessed changes in the SBP, DBP, HR, and SpO₂ until 10 minutes after administering adrenaline-containing lidocaine to patients taking antipsychotic medications, and no significant changes were noted over time in any measurement. This study demonstrates that adrenaline administered at the standard dose for dental treatment under general anesthesia is unlikely to affect the circulation dynamics of regular antipsychotic users.

Adrenaline is a potent stimulant of both α and β adrenergic receptors. α-1 adrenergic receptors are located in vascular and cause smooth muscle constriction. However, β-1 and β-2 receptors are located in the heart and smooth muscle (vascular, bronchial, and gastrointestinal), respectively. Activation of β receptors increases the force and rate of the heart and the relaxation of smooth muscle. The effect of administration of adrenaline in humans is an increase in SBP and HR, while DBP usually decreases. However, when adrenaline is administered in situations where the α-adrenaline receptor has been pharmacologically blocked, β-adrenergic receptors predominate and may lower blood pressure due to vasodilation; this is known as adrenaline reversal [5].

Antipsychotic drugs have an α-adrenergic receptor blocking action. In Japan, lidocaine hydrochloride solution containing adrenaline for dental procedures have precautions for co-administration; adrenaline-containing lidocaine should be administered with caution when co-administered with the antipsychotics, such as butyrophenone, phenothiazine, and atypical antipsychotics. This may be because the dose of adrenaline added to lidocaine for dental treatment is smaller than the dose of adrenaline used for medical purposes. In general, 200 to 1000 μg of adrenaline is used for medical purposes for highly urgent symptoms, such as advanced cardiac life support and severe asthma attacks. Commercially prepared local anesthetics with adrenaline for dental use are available in local anesthetic cartridges, the most common concentration of adrenaline in lidocaine is 1: 80,000 (12.5 μg/mL) in Japan. In this study, a 1.8 mL dental local anesthetic cartridge with an adrenaline concentration of 1:80,000 was administered, for a total dose of 22.5 μg of adrenaline.

Some previous reports have shown a drug interaction between adrenaline and chlorpromazine (phenothiazine antipsychotic). Yagiela et al. [7] reported hemodynamic changes caused by a drug interaction between adrenaline and chlorpromazine in dogs. They found that low-dose adrenaline

(0.33 µg/kg) did not influence blood pressure or heart rate; however, high-dose adrenaline (2.5 µg/kg) induced hypotension and tachycardia. Higuchi et al. [8] also reported intraperitoneal injection of chlorpromazine followed by intraperitoneal injection of adrenaline in rats resulted in marked hypotension and tachycardia depending on the dose of adrenaline; However, administration of chlorpromazine and propranolol, a non-selective beta-blocker, followed by administration of adrenaline only resulted in a slight increase in blood pressure and did not cause a decrease in blood pressure. These animal studies, therefore, provide that hypotension was caused by a drug interaction between adrenaline and chlorpromazine through the activation of the β -adrenergic receptor and showed a dose-dependent effect.

A low-dose adrenaline (0.33 µg/kg) did not cause hemodynamic changes in the study by Yagiela et al. [7], and the result of applying this dose to the average body weight (75.4 kg) of the participating patients in this study was 24.8 µg; this dose is close to the dose in our study (22.5 µg). In addition, it is necessary to consider whether canine doses are comparable to human doses, but our findings are consistent with Yagiela et al. and suggest that there was no change in hemodynamics [7]. These findings suggest that a clinical amount of low dose adrenaline used with lidocaine in dental treatment does not show a strong β -receptor stimulatory effect even when used in patients taking antipsychotics, and does not induce severe hypotension.

The patients taking antipsychotics such as schizophrenia, autism, and intellectual disability are often indicated for dental treatment under general anesthesia because of their noncooperative nature, poor compliance, or dental phobia. The concomitant use of adrenaline and volatile anesthetic can cause increased myocardial irritation and develop cardiac arrhythmias [9, 10]. Therefore, we chose propofol as a general anesthetic agent. In general, propofol affects the cardiovascular system. Propofol does not directly induce bradyarrhythmias because it does not depress sinoatrial node activity or atrioventricular conduction at therapeutic dose [11]. However, propofol shows a simultaneous decrease in heart contractility and afterload reduction, which leads to hypotension. This resulting hypotension involves significant reductions in systolic, diastolic, and mean arterial pressures [12, 13]. Therefore, it is presumed that during general anesthesia with propofol, blood pressure is more likely to decrease due to the interaction between antipsychotics and adrenaline than during common dental treatments.

In this study, we consider that propofol did not enhance blood pressure reduction due to the interaction of antipsychotics with adrenaline because all subjects were ASA I and young, and anesthetic depth was maintained using a BIS monitor. However, it cannot be ruled out that severe hypotension may occur when propofol, antipsychotics, and adrenaline are used in combination in patients with low cardiovascular reserves and/or elderly patients. When using adrenaline-containing lidocaine, it is important to monitor hemodynamics at all times.

Furthermore, remifentanyl, an opioid analgesic, used during anesthesia induction and tracheal intubation in this study can cause hypotension and bradycardia [14]. The context-sensitive half-time (i.e., the time required for the drug's plasma concentration to decrease by 50% after cessation of an infusion) of remifentanyl is short [15]. Therefore, in our protocol, remifentanyl was discontinued immediately after

intubation, and lidocaine with adrenaline was administered 5 minutes after intubation, such that the effect of the circulatory hemodynamic response of remifentanyl was considered negligible at the time of measurement. During dental treatments, the sting from the needle is occasionally associated with systemic complications, such as the vasovagal reflex, ischemic heart disease, and arrhythmias [16]. Even under general anesthesia, it was a possibility that bradycardia was induced by an intense noxious stimulus when infiltrated into the oral submucosa with a large needle, strong pressure, and rapidly by hand [17]. In this study, we believe that a vasovagal reflex was avoided because we performed local anesthesia slowly with a small needle.

This study has some limitations. First, our sample size was relatively small, which may have limited its statistical power. Secondly, among the antipsychotics, the strength of the α_1 receptor blocking action differs for each drug. For example, phenothiazines have a stronger α_1 receptor blocking effect than butyrophenones and atypical antipsychotics [18, 19]. Therefore, we need further rigorous studies to examine the interaction with adrenaline according to each type of antipsychotics.

Conclusion

This is the first prospective study of the effects of the interaction between adrenaline-containing lidocaine and antipsychotics on circulatory dynamics. The injection of commonly used adrenaline-containing lidocaine at clinically-relevant concentrations (12.5 mg/mL) under general anesthesia is unlikely to affect the circulation dynamics of regular antipsychotic users.

Declarations

List of abbreviations: ASA: American Society of Anesthesiologists; DBP: Diastolic blood pressure; HR: Heart rate; SBP: Systolic blood pressure; SpO₂: Percutaneous oxygen saturation

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of The Nippon Dental University School of Life Dentistry Tokyo, Japan (approval number NDU-T-2015-14). It was conducted after clinical trial registration as certified by the International Committee of Medical Journal Editors (trial identification number UMIN000016644). Informed consent: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable.

Availability of data and materials: Reasonable requests for access to the datasets used and/or analyzed during the study can be made to the corresponding author.

Competing interests: The authors declare that they have no competing interests.

Funding: This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions: All authors have read and approved the manuscript. YS: patient recruitment, data collection, writing up draft of the paper. EN: patient recruitment, data collection. GT: data collection, data analysis and interpretation. TK: patient recruitment, data collection. AY: patient recruitment, data collection. KN: revision of draft of the paper. KS: study design, supervision.

Acknowledgments: We thank the research staff at the Department of Dental Anesthesia, The Nippon Dental University Hospital, Tokyo, for their support.

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Figures

Figure 1

Changes in systolic blood pressure (SBP, filled squares) and diastolic blood pressure (DBP, open squares) Error bars represent standard deviation (n=30). No significant differences in SBP and DBP were noted

over time. Baseline; Before adrenaline-containing lidocaine injection. Values are expressed as mean $\pm$ standard deviation. Statistical analysis; Dunnett's test between baseline and at each time point. P-values <0.05 were considered statistically significant

Figure 2

Changes in heart rate (HR, filled circles) over time Error bars represent standard deviation (n=30). No significant differences in HR were noted over time. Baseline; Before adrenaline-containing lidocaine injection. Values are expressed as mean $\pm$ standard deviation. Statistical analysis; Dunnett's test between baseline and at each time point. P-values <0.05 were considered statistically significant

Figure 3

Changes in percutaneous oxygen saturation (SpO₂, filled triangles) over time Error bars represent standard deviation (n=30). No significant differences in SpO₂ were noted over time. Baseline; Before adrenaline-containing lidocaine injection. Values are expressed as mean $\pm$ standard deviation. Statistical analysis; Dunnett's test between baseline and at each time point. P-values <0.05 were considered statistically significant