Cardiovascular Comparison of 2 Types of Local Anesthesia With Vasoconstrictor in Older Adults: A Crossover Study

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We assessed the effect of 2% lidocaine with 1:80,000 adrenaline (L + AD) and 3% prilocaine with 0.03 IU/mL felypressin (P + FP) on blood pressure and heart rate in older adults with systemic diseases undergoing dental extraction. This double-blind, randomized crossover study included 22 elderly participants, aged over 65 years. The participants were administered L + AD for one dental extraction and P + FP for the other. Blood pressure and heart rate were recorded immediately, 5, and 10 minutes after local anesthetic administration and the data were analyzed. The systolic and diastolic blood pressures in the P + FP group increased at all measurement points ($p < .001$). In the L + AD group, the diastolic blood pressure decreased at 5 and 10 minutes after local anesthetic administration ($p < .05$), whereas the heart rate increased at all measured time points ($p < .001$). There were statistically significant differences in systolic blood pressure at 5 and 10 minutes after local anesthetic administration and in diastolic blood pressure and heart rate at all time points between the 2 groups. In older adults, P + FP administration increased the systolic and diastolic blood pressures. L + AD administration increased the heart rate and decreased the diastolic blood pressure.

Key Words: Older adults; Local anesthesia; Blood pressure; Heart rate.

The global population of older adults, defined as aged 65 years or over, was estimated to be 962 million in 2017, and the number continues to rise.¹ The proportion of people aged 65 years or over in Japan is the highest in the world and this rate of change is the fastest worldwide.² In 2010, the rate was 23%, and in 2016, the proportion of older adults in Japan reached 27%.² Older adults tend to have more systemic diseases, with cardiovascular disease being one of the major causes of morbidity and mortality.³ The number of older adults with systemic diseases is also increasing in dental practice. Management of older adults in the dental clinic is challenging because of fluctuating blood pressures and heart rates, and an attentive approach is

required to avoid complications during dental treatment.⁴

Dental local anesthetic solutions contain vasoconstrictors, for example, 2% lidocaine with 1:80,000 adrenaline (L + AD) or 3% prilocaine with 0.03 IU/mL felypressin (P + FP), are both commonly used in Japan and may potentially affect the cardiovascular condition.^{5,6} L + AD, which is one of the most frequently used anesthetics during dental treatment, is known to affect vasoconstriction, cardiac contractility, and heart rate by increasing catecholamine levels.^{7,8} In contrast, the vasopressive action of felypressin (an analogue of vasopressin) does not cause ischemic changes in the myocardium⁹ and has lesser effects on circulatory dynamics than adrenaline.¹⁰ Therefore, felypressin is often used during dental treatment of older adults with cardiovascular diseases.¹⁰ Several findings have been reported regarding the vasoconstrictive action of felypressin^{9,10}; however, these studies were not directed toward participants over the age of 65 years. In this study, we investigated L + AD or P + FP on blood pressure and heart rate in older adults with systemic diseases.

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METHODS

The participants selected were older adults, aged over 65 years, requiring tooth extractions in the Special Care Clinic Outpatient Dental Hospital, Tokyo Medical and Dental University, from November 1, 2016, to December 31, 2017. The patients required extraction of 2 or more maxillary teeth.

Exclusion criteria were as follows: systolic blood pressure ≥ 180 mm Hg, diastolic blood pressure ≥ 110 mm Hg, severe liver disease, severe kidney disease, uncontrolled cardiac arrhythmia, and dementia. Patients could not be in significant acute dental pain.

This study was conducted under the approval of the Tokyo Medical and Dental University Ethics Review Board (D2016-042, UMIN000023236). Informed consent was obtained from all participants.

A blood pressure monitor, electrocardiography bedside monitor, and pulse oximeter (BSM-6301, Nihon Kohden, Tokyo, Japan) were used to record blood pressure, pulse rate, and oxygen saturation.

We used 1 of 2 dental local anesthetic solutions: L + AD (ORA Inj Dental Cartridge®, Showa Chemical Industries, Tokyo, Japan) or P + FP (Citanest-Octapressin®, Dentsply Sirona, Tokyo, Japan). A computer-controlled delivery device (Anaeject II, Nippon Shika Yakuhin Co, Ltd, Yamaguchi, Japan) was used for injection.

Blood pressure and heart rate were measured in the supine position every 2.5 minutes starting 30 minutes before administration of the local anesthetics. The 4 measured values over the last 10 minutes (measured every 2.5 minutes) were considered as the baseline blood pressure and pulse rate. This study analyzed the data at 3 points: at the end of local anesthetic injection (LA0), 5 minutes after local anesthetic injection (LA5), and 10 minutes after local anesthetic injection (LA10).

For one dental extraction, L + AD was used as the local anesthetic; for the other extraction, P + FP was used. The second tooth extraction for the same patient was carried out 5 or more days later following the protocol below, with the only difference being that the other local anesthetic was used. Assignment into the L + AD or P + FP group for the first extraction was performed using a random number table.

The cartridges of the local anesthetic were masked with tape to blind which anesthetic was used, so both the surgeon and the participants were unaware of which solution was being used at each visit. Local anesthesia was performed by a dentist with clinical experience of more than 5 years. Local infiltration of 3.6 mL (2 cartridges) of L + AD or P + FP was performed with a computer-controlled delivery device, Anaeject II. The injection sites were set to 4 points for each tooth: 2

points on the buccal side (mesial side and distal side) and 2 points on the palatal side (mesial side and distal side). We used 1 cartridge (1.8 mL) on the buccal side and 1 cartridge on the palatal side. The total amount of anesthetic agent used in all cases was 3.6 mL.

After administration of the local anesthetic, blood pressure and pulse rate recordings were measured every 2.5 minutes for up to 20 minutes.

We used the visual analogue scale (VAS) to evaluate the anxiety of participants. A 100-mm line was drawn on a blank sheet with the left side marked “No anxiety” and the right side marked “Max anxiety.” We measured VAS at 2 times: just after the participants entered the room and 20 minutes after injection of the local anesthetics.

We used a double-blind randomized crossover study method, with random allocation as to which anesthetic was used at the first visit. The washout period was set to 5 days or more. We conducted a 2-way repeated-measures analysis of variance followed by multiple comparison testing using Shaffer modified Bonferroni correction method (R3.4.3). Power analysis was performed with the G*Power Program.¹¹ Considering $\alpha = 0.05$ and $\beta = 0.8$, the sample size of this study was calculated as 16. It was then increased to 22 to compensate for any potential dropout from the study. Results with descriptive levels (*p* values) lower than .05 were considered statistically significant.

RESULTS

Twenty-two participants (13 males and 9 females) were enrolled in this study; the average participant age was 77.2 years (SD, 6.2 years; range, 65–86 years). At the time of the initial visit, the average systolic blood pressure was 141.6 mm Hg (SD, 16.6 mm Hg; range, 117–173 mm Hg), the average diastolic blood pressure was 80.3 mm Hg (SD, 12.0 mm Hg; range, 60–100 mm Hg), and the average heart rate was 67.0 beats per minute (bpm) (SD, 10.7 bpm; range, 51–98 bpm). There were 14 participants on antihypertensive drugs. Patient information, baseline blood pressure, VAS anxiety results, and tooth extraction sites are summarized in the Table. Room air oxygen saturation was over 96% in all patients.

The systolic blood pressure was increased from baseline after local anesthesia at LA0, LA5, and LA10 in the P + FP group ($p < .01$). On the other hand, the systolic blood pressure was increased from baseline only at LA0 ($p < .05$) in the L + AD group. Also, P + FP increased systolic blood pressure more than L + AD at LA5 ($p < .05$) and LA10 ($p < .001$) (Figure 1).

Clinical Characteristics of the Participants, Teeth Extracted, and Anxiety Scores*

No.	Age, y	Sex	Medication	Baseline BP (mm Hg)		Day 1		Day 2		Day 1		Day 2	
				L + AD	P + FP	Tooth No. (FDI)	Tooth No. (FDI)	VAS 1	VAS 2	VAS 1	VAS 2	VAS 1	VAS 2
1	80	M	Amlodipine	115/62	117/57	17, 21, 22, 25	12, 13, 14, 15	1	1	0	1		
2	73	F	Valsartan-amlodipine combination	150/77	151/76	24, 25	11, 23	1	1	0	1		
3	84	M		140/84	141/80	11, 15, 21	23, 24	1	1	0	1		
4	84	M	Losartan	128/69	130/65	17, 23	23	1	5	0	1		
5	80	M	Nifedipine sustained release, telmisartan	124/80	132/79	14, 15, 16	14, 15	1	0.5	1	3		
6	86	M		136/78	135/74	25	15	4	8.3	1.5	6.4		
7	83	M	Amlodipine-olmesartan combination	150/81	139/76	13, 15, 16	24, 26, 27	9.2	8.5	0.8	4.1		
8	72	F	Azilsartan	113/68	120/67	16, 17	26, 27	0.25	7	0.9	5.3		
9	78	M		143/86	144/88	11, 12, 14	21, 23, 24, 27	1.3	0.7	0.1	0.2		
10	70	F		131/69	112/61	24	23	0.9	2.2	2.8	5.1		
11	65	F		120/68	127/69	13	21, 22	3.6	3	1.1	2.4		
12	81	M		131/67	127/59	16	14	4.5	6.6	0.1	6.7		
13	69	F	Amlodipine	124/67	104/63	11, 21, 23, 24	16, 17	1.4	4	0.1	6.5		
14	68	M	Amlodipine	129/79	129/83	25, 26	11, 12, 22	7.1	4.7	2	1.7		
15	76	F		133/68	129/71	15, 17	11, 12, 22, 25	1.1	1.5	5	6.6		
16	73	F		131/80	130/77	23, 24	16	0.9	2.3	0.2	1.6		
17	80	M	Amlodipine	105/54	120/63	13	11, 12	5	6.7	2.4	5		
18	72	M	Trichlormethiazide, nifedipine	131/71	134/70	25, 27	15, 17	5	4.6	4.7	4.4		
19	83	F	Azelinidipine, imidapril	121/71	106/63	11, 21	27	4.7	6.4	6	8.3		
20	80	M	Olmesartan	134/83	134/76	17	27	1.3	4	0.5	3.5		
21	86	F	Nifedipine sustained release, olmesartan	123/62	136/69	15, 17	11, 13, 23, 26	4.1	4.6	6.2	1.8		
22	87	M	Valsartan-amlodipine combination	123/60	127/60	26	11, 12, 21	0.2	7.5	2.6	5.2		

* Baseline BP indicates blood pressure recorded at last 10 minutes before administration of the local anesthetics (measured every 2.5 minutes); L + AD, 2% lidocaine with 1:80,000 adrenaline; P + FP, 3% prilocaine with 0.03 IU/mL felypressin; FDI, FDI World Dental Federation notation; VAS 1, anxiety rating (cm on 10-cm scale) just after the participants entered the treatment room; VAS 2, anxiety rating (cm on 10-cm scale) 20 minutes after injecting the local anesthetics.

The diastolic blood pressure (Figure 2) was also increased from baseline at LA0, LA5, and LA10 in the P + FP group ($p < .001$). In the L + AD group, there was a decrease in diastolic blood pressure from baseline at LA5 and LA10 ($p < .05$). There was a statistically significant increase in diastolic blood pressure between the P + FP and L + AD groups at all time points ($p < .001$).

Pulse rate was increased from baseline at LA0, LA5, and LA10 in the L + AD group ($p < .001$), but in the P + FP group, there was no significant difference. There was a statistically significant difference in heart rate between the P + FP and L + AD groups at all time points ($p < .001$) (Figure 3).

DISCUSSION

This study showed the effect of L + AD and P + FP on the blood pressure and heart rate of older adults who

underwent dental extraction. To the best of our knowledge, this is the first study to report changes in circulatory dynamics caused by 2 types of local anesthetics in older adults aged over 65 years, many diagnosed with hypertension. The systolic blood pressure was significantly increased in the L + AD group only at LA0, whereas the diastolic blood pressure decreased at LA5 and LA10. In contrast, in the P + FP group, the systolic and diastolic blood pressures were significantly increased at all measured time points after administration of the local anesthetic. Thus, the P + FP group was associated with a significantly greater increase in blood pressure than the L + AD group. However, the L + AD group was associated with a significant increase in heart rate, unlike the P + FP group.

Earlier studies have reported that systolic and diastolic blood pressures were not significantly increased when 1.8 mL of 2% lidocaine with 1:100,000 adrenaline was injected into older patients (average age 60.4 years)

Figure 1. Changes in systolic blood pressure after injection of 3.6 mL of 2% lidocaine with 1:80,000 adrenaline (L + AD) or 3.6 mL of 3% prilocaine with 0.03 IU/mL felypressin (P + FP). The 2-way repeated-measures analysis of variance showed a significant association between time after local anesthetic injection and systolic blood pressure ($p < .01$). The multiple comparison analysis showed that the systolic blood pressure in the P + FP group was significantly increased at all measurement points after local anesthesia compared to the baseline ($p < .001$). On the other hand, the systolic blood pressure was increased from baseline at LA0 ($p < .05$) in the L + AD group; however, it was not significantly increased at LA5 and LA10 compared to the baseline. There was a statistically significant difference in systolic blood pressure between the P + FP and L + AD groups at the time points LA5 and LA10 (LA5: P + FP, 140.8 mm Hg [SD, 12.5 mm Hg; range, 128.3–153.3 mm Hg]; LA5: L + AD, 134.2 mm Hg [SD: 14.5 mm Hg; range, 119.7–148.7 mm Hg]; LA10: P + FP, 142.5 mm Hg [SD, 13.4 mm Hg; range, 129.1–155.9 mm Hg]; LA10: L + AD, 131.5 mm Hg [SD, 13.4 mm Hg; range, 118.1–144.9 mm Hg]). LA0 indicates end of local anesthetic injection; LA5, 5 minutes after local anesthetic injection; LA10, 10 minutes after local anesthetic injection.

with heart disease¹² and in healthy participants.¹³ However, in another study with healthy participants, it was found that systolic blood pressure increased significantly 10 minutes after the administration of lidocaine with adrenaline and diastolic blood pressure decreased significantly.¹⁴ Yet another study with 27 New York Heart Association class III patients showed that dental injection of 1.8 mL of L + AD resulted in a significant increase in systolic blood pressure within 2 minutes after administration.¹⁵ In all these studies, the average age of the participants was less than 65 years.

In our study, the systolic blood pressure in the L + AD group significantly increased at LA0, but no significant change was observed at later points. It is

possible that these changes could be due to differences in systemic diseases, medications, and/or differences in the dose of adrenaline contained in the local anesthetic or the amount of local anesthetic-vasoconstrictor used.

Felypressin acts on the V1 receptor subtypes, resulting in vasoconstriction.^{16,17} However, the dose used for dental treatment does not have a direct effect on the myocardium.¹⁰ P + FP is, however, often used for dental treatment in patients with cardiovascular diseases.¹⁸ An earlier study found that when 3.6–7.2 mL of P + FP was injected in patients with heart disease with an average age of 54.73 years, there was no significant change in blood pressure.¹⁹ However, in another study, it was seen that systolic blood pressure was increased and diastolic

Figure 2. Changes in diastolic blood pressure after injection of 3.6 mL of 2% lidocaine with 1:80,000 adrenaline (L + AD) or 3.6 mL of 3% prilocaine with 0.03 IU/mL felypressin (P + FP). The 2-way repeated-measures analysis of variance showed a significant association between time after local anesthetic injection and diastolic blood pressure ($p < .001$). Diastolic blood pressure in the P + FP group was significantly increased after local anesthesia compared to the baseline ($p < .001$). On the other hand, in the L + AD group, there was a significant decrease in diastolic blood pressure at LA5 and LA10 compared to the baseline ($p < .05$). There was a statistically significant difference in diastolic blood pressure between the P + FP and L + AD groups at all time points (LA0: P + FP, 78.7 mm Hg [SD, 8.8 mm Hg; range, 69.9–87.5 mm Hg]; LA0: L + AD, 69.6 mm Hg [SD, 7.8, range 61.8–77.4 mm Hg]; LA5: P + FP, 78.7 mm Hg [SD, 8.9 mm Hg; range, 69.8–87.6 mm Hg]; LA5: L + AD, 68.2 mm Hg [SD, 9.5 mm Hg; range, 58.7–77.7 mm Hg]; LA10: P + FP, 77.8 mm Hg [SD, 8.4 mm Hg; range, 69.4–86.2 mm Hg]; LA10: L + AD, 69.2 mm Hg [SD, 9.7, range 59.5–78.9 mm Hg]). LA0 indicates end of local anesthetic injection; LA5, 5 minutes after local anesthetic injection; LA10, 10 minutes after local anesthetic injection.

blood pressure was decreased 3 minutes after injection of 3.6 mL of P + FP in hypertensive participants.²⁰ Cáceres et al¹⁹ compared lidocaine without adrenaline and P + FP in patients with cardiac disease, and no difference in blood pressure changes after local anesthesia was reported. In our study, P + FP increased both systolic and diastolic blood pressure. This variation could possibly be due to increased peripheral vascular resistance,²⁰ modulated by the pharmacological action of the vasoconstrictor, or other factors such as preprocedure pain, pain from injection, or the effect of systemic diseases or medication used. There is a possibility that arteriosclerosis due to aging may have an effect on the results as well.

Meral et al¹³ studied the adverse hemodynamic effects and plasma concentrations of lidocaine and epinephrine in healthy patients. The local anesthetic solutions used in their study were 2.0 mL of 2% lidocaine with 1:100,000 epinephrine or 2.0 mL of plain 2% lidocaine. They indicated that increase in heart rate was recorded immediately after the injection (3 minutes) in both groups.¹³ Our analysis method and results are different from this previous research.

We believe our study is the first crossover study to evaluate the cardiovascular effects of different vasoconstrictors on older adults. Adrenaline is known to increase the heart rate by stimulating β_1 adrenergic receptors, and this action was directly observed in our

Figure 3. Changes in heart rate after injection of 3.6 mL of 2% lidocaine with 1:80,000 adrenaline (L + AD) or 3.6 mL of 3% prilocaine with 0.03 IU/mL felypressin (P + FP). The 2-way repeated-measures analysis of variance showed a significant association between time after local anesthetic injection and heart rate ($p < .001$). In the multiple comparison analysis, the heart rate increased at all measured time points after local anesthesia in the L + AD group compared to the baseline ($p < .001$). The P + FP group showed no significant association with heart rate at all measured time points. There were statistically significant differences in heart rate between the P + FP and L + AD groups at all time points (LA0: P + FP, 78.7 beats per minute [bpm] [SD, 8.8 bpm; range, 69.9–87.5 bpm]; LA0: L + AD, 69.6 bpm [SD, 7.8 bpm; range, 61.8–77.4 bpm]; LA5: P + FP, 78.7 bpm [SD, 8.9 bpm; range, 69.8–87.6 bpm]; LA5: L + AD, 68.2 bpm [SD, 9.5 bpm; range, 58.7–77.7 bpm]; LA10: P + FP, 77.8 bpm [SD, 8.4 bpm; range, 69.4–86.2 bpm]; LA10: L + AD, 69.2 bpm [SD, 9.7 mm Hg; range 59.5–78.9 bpm]). LA0 indicates end of local anesthetic injection; LA5, 5 minutes after local anesthetic injection; LA10, 10 minutes after local anesthetic injection.

study in the L + AD group. For older adults, the effect of adrenaline may be more pronounced.

Our study adjusted for differing participant characteristics by its crossover study design. In addition, by using a computer-controlled delivery system for anesthetic injections and having experienced dental practitioners administer the local anesthesia, we attempted to minimize injection discomfort as much as possible, which may have influenced cardiovascular parameters. However, our study has some limitations. First, this study did not evaluate preprocedure pain, which is known to affect blood pressure and heart rate. However, we extracted teeth without clinically acute symptoms and inflammation. In our study, we did not see significant differences in baseline blood pressure

and heart rate at the 2 different sessions. For that reason, we believe that acute dental pain was not a confounding factor. Second, we were able to adjust for participants' variable medical and psychological characteristics by using a crossover design, but we did not evaluate the effects of individual systemic diseases or drugs. In this study, 8 of 22 participants were not taking antihypertensive agents. Although we measured the average $\pm$ SD of the blood pressure and heart rate for participants taking/not taking antihypertensive agents, we were not able to detect a statistical significance based on this parameter because of the small number of participants. In the future, there is a need to investigate the effects of hypertension medications on the control of blood pressure and heart rate

in relation to vasoconstrictor use. In our study, heart rate was increased by about 10 bpm, but this did not cause overt tachycardia (heart rate >100 bpm). This change may not be clinically significant for many patients. However, local anesthetics without adrenaline are recommended in patients with severe heart disease, such as unstable angina, severe valvular disease, certain dysrhythmias, or advanced congestive heart failure. For patients with paroxysmal atrial fibrillation, local anesthetics containing adrenaline may promote an acute episode of atrial fibrillation. Another limitation of our study was that the local anesthetic agents and vasoconstrictors used were both different for the 2 groups. Unfortunately, 2% lidocaine is not commercially available with 0.03 IU/mL felypressin nor 3% prilocaine with 1:80,000 epinephrine.

CONCLUSIONS

P + FP significantly increased systolic and diastolic blood pressure for 10 minutes after dental local anesthetic administration in older adults over 65 years more than those administered L + AD. Systolic blood pressure was elevated for only a short time after local anesthetic administration in the L + AD group whereas diastolic pressure decreased shortly after injection. However, there was a significant increase in heart rate associated with lidocaine-adrenaline averaging 10 bpm, but not with prilocaine-felypressin. For older adults (>65 years) receiving dental treatment, lidocaine-epinephrine local anesthesia may be optimal when an increase in blood pressure should be avoided, and prilocaine-felypressin may be more suitable when tachycardia is undesirable. Further research is necessary to obtain reliable information for selecting safe local anesthetics for use in dental treatment in older adults with cardiovascular disease.

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