The Potential of the Nasal Mucosa Route for Emergency Drug Administration Via a High-Pressure Needleless Injection System

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It is often difficult to expeditiously establish an intravenous (IV) route in a medical emergency, and alternatives to an IV route may also be difficult for many dentists to accomplish. The purpose of this article is to demonstrate that without the necessity of advanced training, the nasal mucosa route of administration is a promising alternative to the IV route in an emergency without complications, and will also show that epinephrine can be quickly absorbed into systemic circulation from the nasal mucosa. Ten beagle dogs were administered 400 μg of epinephrine in the nasal septal mucosa. The mean peak value of the plasma epinephrine (20.1 ± 12.4 ng/mL) was obtained after 15 seconds, and the peak systolic pressure was 200% of the control value after 60 seconds. Although the dose of epinephrine must be considered because blood flow decreases during cardiopulmonary resuscitation, this method presents a promising alternative to the IV route.

Key Words: IV alternative; Epinephrine; CPR.

Although few dentists have performed cardiopulmonary resuscitation (CPR), considering the number of dental patients seen in a typical clinic, the possibility cannot be ignored that CPR might become necessary during clinical dental treatment. During CPR, intravenous (IV) injection of various drugs, such as epinephrine, may be necessary; however, it is difficult for dentists with no special training to expeditiously establish an IV access route and administer drugs to patients with circulatory collapse. In such circumstances, several alternative emergency administration routes have been reported.[1–4] However, traditional alternative administration routes are not necessarily effective for most dentists due to complications or technical restrictions.[2,5] The purpose of this study was to show that it is possible in beagle dogs to expeditiously transfer epinephrine from the nasal mucosa to the general circulation using dental needleless injectors and that the nasal mucosa is useful as a simple alternative emergency administration route.

METHODS

This experiment was performed using the handling regulations of experimental animals at Aichi-Gakuin University. Ten adult beagles weighing 11.0 ± 1.7 kg were used for a study group and another 10 beagles weighing 10.7 ± 1.9 kg for a control group. Anesthesia was induced with thiamylal and succinylcholine chloride intravenously and maintained by the semiclosed circuit after intubation. Ventilation was controlled with nitrous oxide–oxygen–isoflurane (1%) and vecuronium. The tidal volume was adjusted to 150–200 mL based on weight, and $P_{ET}CO_2$ was maintained at 32–40 torr.

After the induction of anesthesia, an IV access route was established in an upper limb. Left and right femoral artery cannulations were performed percutaneously to measure blood pressure on one side and to collect blood from the other side. After finishing this preparation, the dog was allowed to equilibrate for more than 30 minutes to obtain stability of the circulatory system. Then, 0.4 mL (400 μg) of 1 mg/mL of epinephrine for the study group and 0.4 mL of physiological saline for the control group was placed into an emptied dental cartridge and administered to the nasal septum mucosa via a needleless injector.

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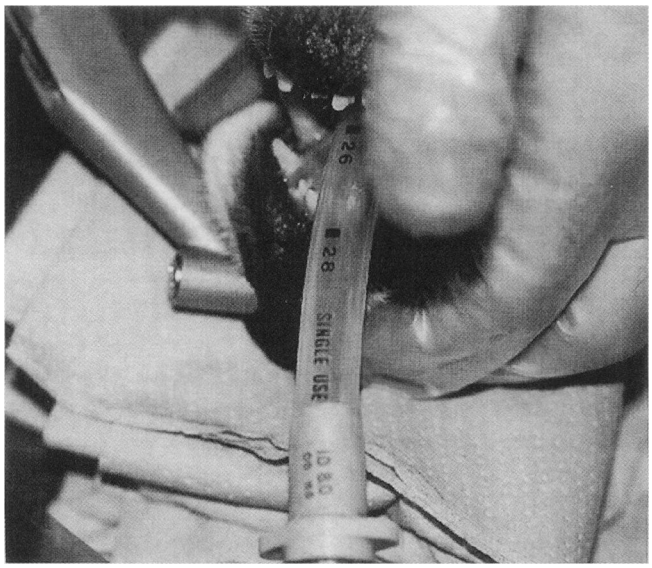

Figure 1. The injection surface of a needleless injector is placed in close contact with the nasal septum surface. Simultaneously, the septum is pressed from the opposite nasal foramen with a finger so the injection pressure on the mucosa does not escape.

The injection surface of a needleless injector (SyriJet, Mizzy, Cherry Hill, NJ) was placed in close contact with the nasal septum surface 2.5 cm away from the apex of the nose. Simultaneously, the nasal septum was pressed from the opposite nasal foramen with a finger, and then epinephrine was injected so that the injection pressure on the mucosa did not escape (Figure 1). The maximum injection volume of the SyriJet is 0.2 mL, so we immediately injected again to attain the 0.4-mL volume, for a total of 2 injections.

For the measurement of the circulatory system of both groups, systolic blood pressure, diastolic pressure, and heart rate were recorded just before injection and 15, 30, 60, 90, 120, 180, and 300 seconds after injection. In 6 dogs from the study group, 4 mL of blood was collected from the artery to measure catecholamines simultaneously with the recording of the circulatory parameters. The collected blood was cooled and centrifuged as promptly as possible, and the blood plasma was preserved at −40°C until the measurement. A respirator (SN–480-3, Shinano, Tokyo, Japan), an OIR-7101 (Nihon Koden Corp, Tokyo, Japan) to measure $P_{ET}CO_2$, the Life Scope 8 (Nihon Koden Corp, Tokyo, Japan) to measure the circulatory system, the SyriJet injector, and high-performance liquid chromatography to measure catecholamines were used.

RESULTS

Changes in blood pressure are shown by percentage change, taking the value just before injection as 100%. In the study group, the pulse rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure before administration were 118 ± 22/min, 109 ± 17 torr, 57 ± 11 torr, and 74 ± 12 torr, respectively. In the control group, the pulse rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure before administration were 116 ± 28/min, 104 ± 18 torr, 54 ± 11 torr, and 70 ± 14 torr, respectively. Arrhythmias were not observed during the experiment period in all dogs.

In the study group, both systolic and diastolic blood pressure started increasing 15 seconds after administration and reached a plateau exceeding 200% of the control value. This plateau continued for 2 minutes. There was almost no change in the pulse rate during the entire measurement period (Figure 2). In the control group, there was almost no change in the circulatory parameters except for a small increase (not statistically significant) in systolic and diastolic blood pressure in 15 seconds after injection (Figure 3). The increased rate of plasma concentration of epinephrine in the study group was extremely high, reaching the peak value 15 seconds after administration, and gradually decreased over time (Figure 4).

DISCUSSION

The number of times that CPR has been performed in the dental setting is unknown, because there have been no exact statistical data. However, considering the high prevalence rate for dental diseases, the possibility cannot be ignored that CPR could be necessary during dental treatment. Intravenous drug administration is a highly reliable and certain method to use during CPR; however, because peripheral blood vessels may not be palpable in patients with circulatory collapse, easy and expeditious establishment of an IV route cannot always be expected. According to one report of prehospital cardiopulmonary collapse in children, the success rate of establishing a peripheral venous access route was only 18%, even by physicians in the emergency department.[1]

Cut down is basically a time-consuming method.[2] The success rate of central venous access is not always high without sufficient continuous training, and severe complications often occur.[2] During CPR, time is extremely precious, and it is undesirable to use several minutes merely to establish an IV route. Therefore, in cases where establishment of an IV access route is difficult, several alternative routes, such as subcutaneous, intralingual, intracardiac, intraosseous, intramuscular, and intratracheal routes, have been reported. However, subcutaneous and intralingual administrations are ineffec-

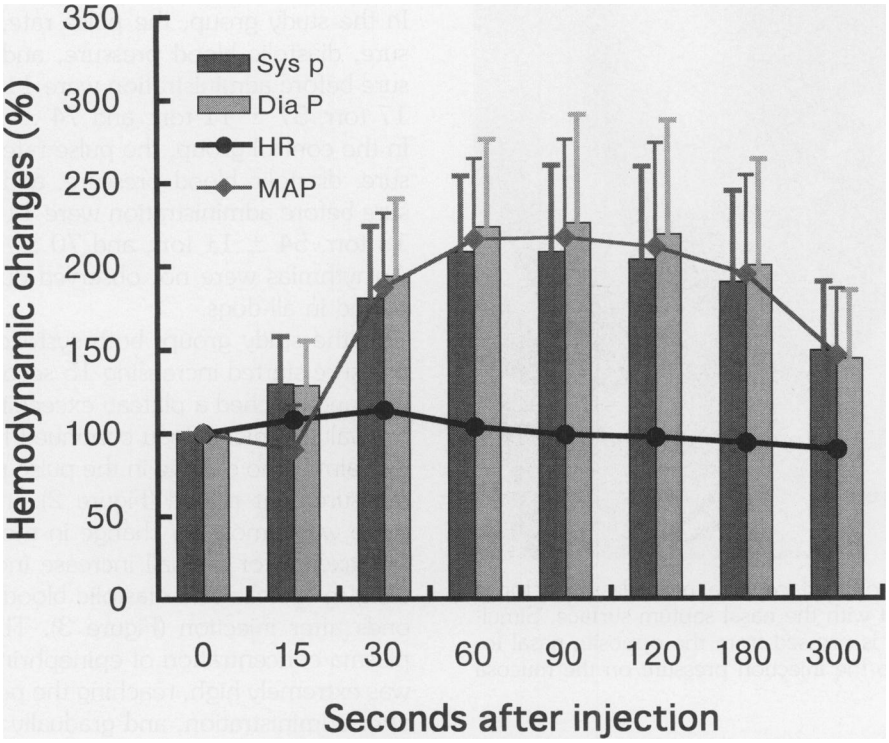

Figure 2. Hemodynamic changes in the study group are shown by percent (preinjection value = 100). Heart rate (HR) at 30 seconds only demonstrated significant increase. Systolic blood pressure (Sys P), diastolic blood pressure (Dia P), and mean arterial pressure (MAP) demonstrated significant increase at all measurement points except MAP at 15 seconds (Wilcoxon test, $P < .05$, $n = 10$). Marked points represent mean ± SD.

tive.[3] Intracardiac administration easily causes fatal complications, such as cardiac tamponade and coronary artery and myocardial laceration,[4,5] and is a difficult route of administration to perform. Although good results with intraosseous administration in pediatric cases were reported,[6,7] there have been no reports of adult cases, and training to learn the puncture process is necessary. Considering the high density of adult bones, this could be a time-consuming procedure.

Intramuscular administration is an effective administration route of epinephrine for anaphylaxis, but it requires 5 minutes to reach a peak plasma level, and its maximum plasma level is not thought to be enough for CPR.[8] Intratracheal administration is thought to be the most effective alternative administration route[9,10]; however, most dentists have not been trained to perform expeditious endotracheal intubation in emergency situations. Therefore, an administration route that is appropriate to the education and training that most dentists receive is obviously necessary.

Because the nasal mucosa has the advantage of drug absorption from a rich blood flow and no first-pass effect,[11] it has been used as an administration route for hypotensive drugs[12] and premedication before anesthesia.[13] However, because epinephrine has a strong vasoconstriction effect on local blood vessels, a sufficient increase in its concentration in blood is not obtainable by topical administration. Because dental needleless injectors like the SyriJet can administer drugs in tissue by applying them under pressure, the possibility exists that they can transfer a sufficient amount of epinephrine into the blood before its vasoconstrictive effects occur. Actually, as described in the "Results" section, epinephrine concentration in the blood reached a peak 15 seconds after administration. This showed that pressure administration from the nasal mucosa could expeditiously transfer an amount of epinephrine sufficient to cause a rise in blood pressure.

The primary advantages of using the nasal mucosa as an alternative emergency administration route are the minimal training required and the use of emptied local anesthetic cartridges filled with epinephrine. This method can be immediately performed in dental clinic rooms where preparation for an emergency is not always the same as in operating rooms or intensive care units. Moreover, because dentists use this method when performing treatment in the facial region, they can perform this method with less hesitation in this region compared with other regions (eg, intracardiac administration). Also, severe complications did not occur. (Possible com-

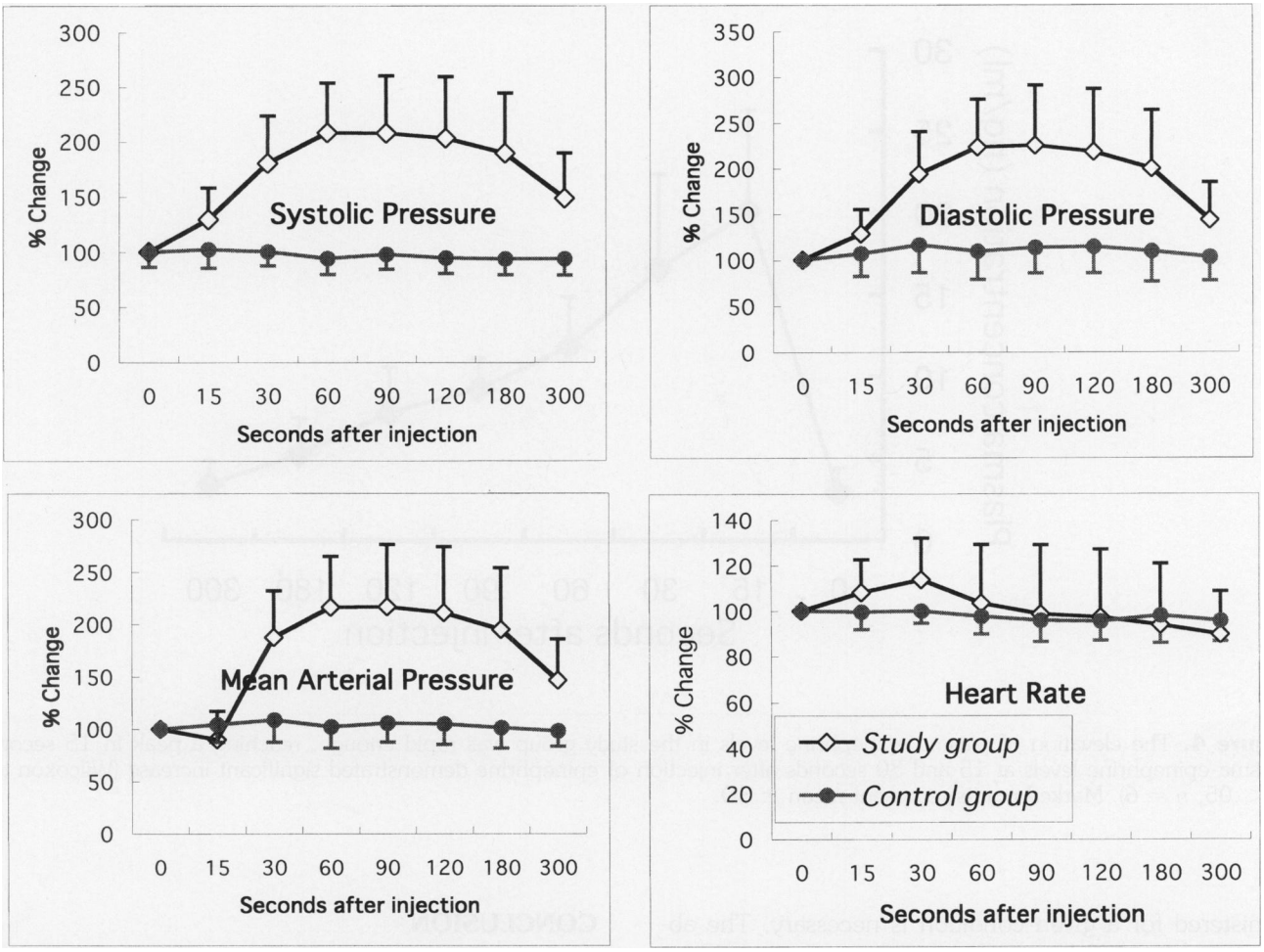

Figure 3. Hemodynamic changes in both groups are shown by percent (preinjection value = 100). Heart rate (HR) in both groups remained almost unchanged, and the difference between the groups was not apparent or statistically significant. Systolic blood pressure (Sys P), diastolic blood pressure (Dia P), and mean arterial pressure (MAP) in the study group demonstrated significantly high values in all measurement points except at 15 seconds of MAP (Mann-Whitney *U* test, $P < .05$, $n = 10$). Marked points represent mean ± SD.

plications caused by injection pressure and the high concentration of epinephrine can occur; however, only a small amount of bleeding was observed in the study group.) The application of this method to patients with asthma or allergic reaction may also be considered, except for severe cases that require endotracheal intubation for airway maintenance.

Before this method is clinically applied, it may be useful to look more closely at some of its features. Although the baroreceptor reflex control of heart rate is generally suppressed by inhalation anesthetics, the suppression by isoflurane is weaker than that of halothane or enflurane.[14] The heart rate regulation mechanism of the dogs' baroreceptor reflex is suppressed by the inhalation of 2.6% isoflurane but not 1.3%.[15]

Only 1.0% isoflurane was used in this experiment. Therefore, it may be considered that the unchanged heart rate was due to the heart rate regulation of the baroceptor reflex, as was observed in the clinical situation.

The relatively short duration of epinephrine effects may make additional injection necessary. When additional administration is necessary, another site should be chosen because absorption via nasal mucosa cannot be expected due to the peripheral blood vessel contractile effect of the epinephrine administered already. Therefore, the opposite nostril should be chosen instead for injection. Another candidate for injection is the hard palate mucosa where the blood vessels are located between the injection site and bone and the pressure at injection does not escape.

Finally, evaluation of the amount of epinephrine ad-

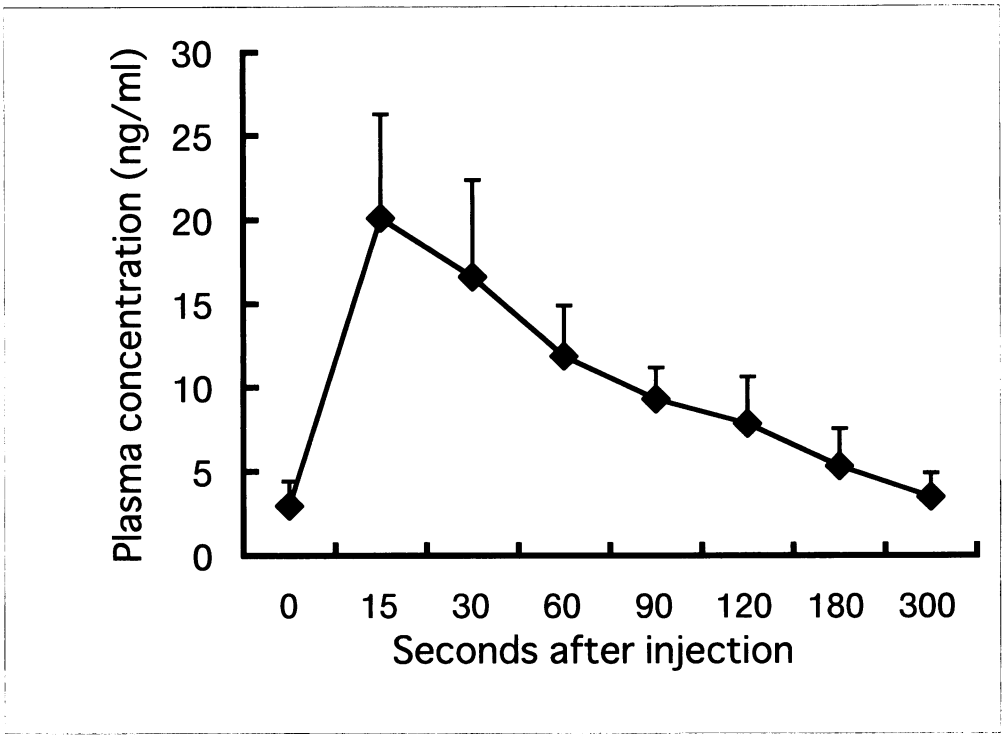

Figure 4. The elevation of plasma epinephrine levels in the study group was rapid enough, reaching a peak in 15 seconds. Plasma epinephrine levels at 15 and 30 seconds after injection of epinephrine demonstrated significant increase (Wilcoxon test, $P < .05$, $n = 6$). Marked points represent mean ± SD.

ministered for a given condition is necessary. The absorption of epinephrine administered in the nasal mucosa greatly depends on local blood flow, and an approximately 60% increase in blood flow was observed under inhalation anesthesia compared with that during an unanesthetized state.[16] During external cardiac massage, the amount of blood flow was approximately one third of that during normal circumstances.[17]

This experiment was performed under conditions in which blood flow was approximately 5 times greater (1/[1.6 × 1/3]) than what was expected in external cardiac massage. Whichever administration route is selected during cardiac arrest, if effective cardiac massage must be performed to maintain at least a necessary minimal amount of blood flow for absorption and systemic distribution, resuscitation does not succeed. This method, in which drug absorption depends on blood flow in the nasal mucosa, is greatly influenced by decrease in local blood flow. Therefore, although 400 μg was an effective amount in this experiment, it might be of questionable efficacy during cardiac arrest and CPR. Therefore, it is necessary to evaluate the effective dose of intranasal administration of epinephrine using experimental models with decreased blood flow in the nasal mucosa or cardiac arrest models.

CONCLUSION

The peak concentration of administered epinephrine in blood was obtained 15 seconds after intranasal injection, and a marked rise in blood pressure (200%) was observed 60 seconds afterward, which showed that epinephrine is expeditiously absorbed from the nasal mucosa of the anesthetized beagle dog model. Although it is necessary to evaluate the epinephrine dose under conditions of cardiac arrest or low blood flow, this method of administering epinephrine to the nasal mucosa using dental needleless injectors is promising as an alternative emergency administration route.

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