Effect of Epinephrine on the Absorption of Lidocaine Following Application to the Oral Mucosa in Rats

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Research Article

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Abstract

Objective

We investigated the role of epinephrine in prolonging the localization of a topical anesthetic on oral mucosa and inhibiting its absorption in blood.

Methods

We used 7–8-week-old specific-pathogen-free Wistar male rats (n = 128) for our study. We divided them into lidocaine and lidocaine with epinephrine groups and applied 5 μL of ^{14}C-labeled lidocaine hydrochloride gel and 10 μg/mL ^{14}C-labeled lidocaine hydrochloride gel with added epinephrine to the palatal mucosae of the rats, respectively. The amount of lidocaine was measured by radioactivity and was observed using autoradiograms.

Results

After 4 min, the values were significantly lower in the lidocaine with epinephrine group (1040.0 ± 142.8 vs. 701.2 ± 109.0 ng/mg [20 min]). After 40 min, the lidocaine level became significantly higher in the lidocaine with epinephrine group (586.8 ± 112.4 vs. 1131.3 ± 155.2 ng/mg [40 min]). Similar results were observed in the palatine bone and mucosa and serum.

Conclusion

Epinephrine prolonged the localization of lidocaine applied to the mucosa and inhibited its absorption into the bloodstream. Clinical studies are required to evaluate the use of epinephrine-containing topical anesthetics on the oral mucosa.

Introduction

Dental topical anesthetics are not only used to numb the injection site but also for minor soft tissue surgeries,[1,2] extractions,[3,4] and suppression of the gag reflex.[5] Lidocaine, which is a widely used injectable local anesthetic, is also used as a topical anesthetic. However, due to its short-acting nature, the duration of anesthesia may be inadequate. The oral soft tissues have a rich network of capillaries that causes rapid absorption of lidocaine after its application. This large dose of lidocaine may result in systemic toxicity. The application of large doses of benzocaine, which is also widely used as a dental topical anesthetic, to the oral mucosa causes methemoglobinemia.[6] These side effects can be prevented by inhibiting local anesthetic absorption, which can be achieved by inducing the contraction of local blood vessels. Epinephrine, which has a powerful vasoconstrictive effect, is added to dental lidocaine

injections for this purpose. However, as the mucosal permeability of epinephrine is low,[7] its addition to topical anesthetics neither extends the duration of anesthetic action nor prevents its rapid absorption from the mucosa.[7–10] Therefore, dental topical anesthetics containing epinephrine are not currently used. In the past, tetracaine and cocaine with added epinephrine were widely used as topical anesthetics for the skin.[11,12] Subsequently, a topical anesthetic containing lidocaine, tetracaine, and epinephrine was developed, and studies were conducted to determine its efficacy and safety.[13,14] The efficacy of other cutaneous topical anesthetics has also been studied,[15,16] and the addition of epinephrine has been regarded as an effective method of obtaining a sufficient anesthetic effect.[17] Therefore, a reinvestigation of the effect of epinephrine containing topical anesthetics on the oral mucosal surface is required. However, no specific study has yet fully explored this effect. Intra-oral injections would be more comfortable and safer if epinephrine could increase the topical anesthetic effect. Capillaries running immediately beneath the mucosa, which lacks a cornified epithelium, are believed to be more susceptible to the effect of epinephrine than those under the skin. Therefore, we hypothesized that epinephrine prolongs the anesthetic effect of topical lidocaine on oral mucosa. The primary outcome of this study was the amount of lidocaine in rat oral mucosa and serum when the topical anesthetic was used with added epinephrine.

Methods

This study was approved by the Animal Experiment Committee of the Nippon Dental University School of Life Dentistry (approval No. 10–29) and was conducted in accordance with the guidelines laid down by ARRIVE (Animal Research: Reporting of in vivo Experiments).

Animals

One hundred and twenty-eight 7–8-week-old specific-pathogen-free Wistar male rats (Tokyo Laboratory Animals Science Co., Ltd., Tokyo, Japan) were used for this study. We divided the rats into 2 groups: the lidocaine group and lidocaine with epinephrine group. Each group included 64 animals. Two rats per cage were housed in the animal room of the University's isotope facility and were given unrestricted access to water and food.

Formulation of test drugs

We dissolved 3.5 g of carboxymethyl cellulose (CMC) sodium salt in 100 mL of 2% lidocaine hydrochloride solution to formulate a 2% lidocaine hydrochloride gel. The test drugs were then formulated using the following methods:

(a) 2% ^{14}C-labeled lidocaine hydrochloride gel

We added 25 μL of ^{14}C-labeled lidocaine hydrochloride (American Radiolabeled Chemicals, Inc., St. Louis, MO, USA) and 0.5 μL of 0.9% sodium chloride (NaCl) to 500 μL of 2% lidocaine hydrochloride gel to

prepare 525.5 µL of 2% ^{14}C-labeled lidocaine hydrochloride gel (specific activity 43.1 MBq/mmol, radioactivity concentration 1.5 MBq/mL).

(b) 10 µg/mL 2% ^{14}C-labeled lidocaine hydrochloride gel with added epinephrine

We used 0.5 µL of 1 mg/mL epinephrine in place of 0.5 µL of 0.9% NaCl as used in (a) to prepare 10 µg/mL of 2% ^{14}C-lidocaine hydrochloride gel.

Indigo carmine dye was added into the test drug to aid visibility.

Lidocaine measurement

Lidocaine was measured according to the method described by Akimoto et al.[18]

(a) Sample collection

Rats were administered pentobarbital (50 mg/kg) intraperitoneally for inducing sleep and were placed on their backs. A 5 µL dose of both the test drugs was applied to the oral mucosae of the animals of corresponding test groups using an applicator tip with an internal diameter of 2 mm and a length of 4 mm. This drug application was at the intersection of the midline of the palate and a line joining the centers of the bilateral second molars. Samples of the maxilla and mucosa were collected from 100 rats, serum was collected from 24 rats, and autoradiographs were recorded for 4 rats.

(i) Maxillary tissue

One hundred rats (50 rats from each study group of lidocaine and lidocaine with epinephrine) were used for tissue measurement. At 0.5, 2, 4, 7, 10, 20, 30, 40, 50, and 60 min after application (total 10 time points), sleeping rats were decapitated with a guillotine and the gel remaining on the surface of the mucosa was removed with cotton swabs. Thus, there were 5 samples at each time point. The drug-applied region was excised from the upper jaw using bone scissors, and the mucosa was separated from the bone using bone forceps. These samples of the mucosa and bone were minced with the bone scissors for radioactivity measurement.

(ii) Serum

Another 24 rats (12 rats from each study group of lidocaine and lidocaine with epinephrine) were used for serum evaluation. At 0.5, 2, 5, 10, 20, 30, 40, 50, and 60 min after application, 0.4 mL blood was collected from the left femoral artery and centrifuged at 4°C and 15,000 × g for 20 min to obtain serum. Thus, 9 blood samples for each time point were collected from each rat of both the groups. The study animals were euthanized by intraperitoneal administration of 150 mg/kg pentobarbital sodium after sample collection.

(b) Radioactivity measurements

The collected samples of the maxillary tissue (10–50 mg) or serum (50 µL) were placed in a liquid scintillation counter vial, and 0.5 mL of tissue solubilizer (Solvable®; PerkinElmer, Waltham, MA, USA) was added. This mixture was warmed and agitated at 60°C for 2 h, and 25 µL of acetic acid was added to neutralize it.

To this solution, a liquid scintillation cocktail (AQUASOL-2®; PerkinElmer, Waltham, MA, USA) was added, and the resulting solution was left in the dark for 24 h. Thereafter, the radioactivity (dpm) was measured using a liquid scintillation counter (LEC-6100; Aloka, Tokyo, Japan).

The amount of lidocaine in the mucosa or palatine bone was calculated per wet weight of tissue (ng/mg wet weight) from the measured value and specific activity. The amount of lidocaine in the serum was indicated in terms of ^{14}C-radioactivity (dpm/mL).

Autoradiography observations

Autoradiography was conducted according to the method described by Hashimoto *et al.*[19]

(a) Section preparation

Remaining 4 rats (2 rats from each study group of lidocaine and lidocaine with epinephrine) were used for autoradiography. Same method of lidocaine measurement was followed as in the previous section. The maxilla was removed 10 and 40 min after lidocaine or lidocaine with epinephrine application, embedded in CMC, and placed on hexane dry ice to prepare frozen maxillary tissue blocks. A cryomicrotome (CM4050S®; Leica Microsystems, Wetzlar, Germany) was then used to prepare coronal sections of 10 µm thickness. These sections were placed on an adhesive sheet (Transfer Film®; Leica Microsystems, Wetzlar, Germany) and dried.

(b) Film observations

The dried sections were pressed onto an x-ray film (BioMax® XAR Film; Kodak, Rochester, NY, USA) and exposed to a temperature of -80ºC for 40 days. The developed films were placed on sections stained with 0.25% eosin (EosinY®; Nacalai Tesque Inc., Kyoto, Japan), and the radioactive isotope distribution was observed using a transmission scanner (GT9500®; EPSON, Nagano, Japan).

Statistical analyses

Measurements are indicated as means ± standard deviations. Measurements at each time point were compared between the 2 groups using an unpaired t-test or Welch's t-test if unequal variance was observed, with $p < 0.05$ regarded as significant. A software was used for statistical analyses (IBM SPSS® Statistics ver. 25; IBM Japan Ltd., Tokyo, Japan).

Results

Lidocaine measurements

(a) Palatal mucosa

There was no significant difference in the lidocaine levels in the first 2 min between the lidocaine and lidocaine with epinephrine groups. However, after 4 min and up to and inclusive of 20 min, lidocaine values were significantly lower in the lidocaine with epinephrine group than in the other group. After 30 min, this significant difference was no longer evident. However, after 40 min, the lidocaine level was once again significantly higher in the lidocaine with epinephrine group than in the other group (Table 1).

Table 1

Amount of ^{14}C-lidocaine in the palatal mucosa

	Lidocaine mean ± SD	**Lidocaine with epinephrine mean ± SD**	***p*-value**
Sample size	5	5	
Time(min)			
0.5	371.5 ± 48.4	423.9 ± 71.2	0.210
2	751.9 ± 133.8	669.8 ± 101.6	0.306
4	813.5 ± 41.2	612.2 ± 56.2	< 0.001
7	948.3 ± 104.9	583.7 ± 47.5	< 0.001
10	1216.6 ± 156.7	658.5 ± 92.0	< 0.001
20	1040.0 ± 142.8	701.2 ± 109.0	0.003
30	940.1 ± 144.2	881.0 ± 84.7	0.452
40	586.8 ± 112.4	1131.3 ± 155.2	< 0.001
50	481.0 ± 53.2	995.2 ± 156.4	< 0.001
60	306.6 ± 109.0	621.5 ± 137.7	0.004
Data presented as the mean amount of lidocaine in ng/1 mg mucosa			
Abbreviations: SD, standard deviation			
p-value compares lidocaine versus lidocaine with epinephrine			
unpaired t-test used to compare means			

(b) Palatine bone

There was no significant difference in the lidocaine levels in the first 4 min between the lidocaine and lidocaine with epinephrine groups. However, after 7 min and up to and inclusive of 20 min, the lidocaine values were significantly lower in the lidocaine with epinephrine group than in the other group. From 30

min, the lidocaine levels were significantly higher in the lidocaine with epinephrine group than in the other group (Table 2).

Table 2
Amount of ^{14}C-lidocaine in the palatal bone

	Lidocaine mean ± SD	**Lidocaine with epinephrine mean ± SD**	***p*-value**
Sample size	5	5	
Time(min)			
0.5	1.8 ± 0.4	1.9 ± 0.5	0.738
2	3.9 ± 0.6	4.3 ± 0.6	0.378
4	3.1 ± 0.9	2.9 ± 0.6	0.769
7	5.2 ± 0.5	3.6 ± 0.9	0.011
10	10.3 ± 2.2	3.7 ± 0.6	0.002
20	7.4 ± 0.8	4.4 ± 0.6	< 0.001
30	4.3 ± 0.8	6.8 ± 0.6	0.001
40	3.4 ± 0.7	9.9 ± 1.2	< 0.001
50	2.6 ± 0.6	6.6 ± 0.6	< 0.001
60	1.7 ± 0.8	3.5 ± 0.8	0.008
Data presented as the mean amount of lidocaine in ng/1 mg bone			
Abbreviations: SD, standard deviation			
p-value compares lidocaine versus lidocaine with epinephrine			
unpaired t-test or Welch's test if unequal variance used to compare means			

(c) Serum

There was no significant difference in the lidocaine levels in the first 5 min between the lidocaine and lidocaine with epinephrine groups. However, after 5 min, and up to and inclusive of 20 min, the lidocaine levels were significantly lower in the lidocaine with epinephrine group than in the other group. After 30 min, this difference was no longer significant, although after 40 min, the lidocaine values were significantly higher in the lidocaine with epinephrine group (Table 3).

Table 3

Radioactivity of ^{14}C-lidocaine in the serum

	Lidocaine mean ± SD	**Lidocaine with epinephrine mean ± SD**	***p*-value**
Sample size	12	12	
Time(min)			
0.5	19.1 ± 9.2	15.6 ± 6.7	0.291
2	21.8 ± 10.4	24.8 ± 5.6	0.383
5	34.1 ± 9.5	30.7 ± 6.6	0.322
10	55.9 ± 4.3	40.9 ± 4.8	< 0.001
20	76.9 ± 8.2	48.4 ± 8.6	< 0.001
30	63.4 ± 7.8	59.8 ± 4.7	0.189
40	49.3 ± 5.7	70.2 ± 4.4	< 0.001
40	3.4 ± 0.7	9.9 ± 1.2	< 0.001
50	2.6 ± 0.6	6.6 ± 0.6	< 0.001
60	1.7 ± 0.8	3.5 ± 0.8	0.008
Data presented as the mean of ^{14}C radioactivity in dpm/1mL serum			
Abbreviations: SD, standard deviation			
p-value compares lidocaine versus lidocaine with epinephrine			
unpaired t-test used to compare means.			

Film observations

When epinephrine was added, the amount of radioactivity was lower after 10 min and higher after 40 min compared with that of lidocaine alone (Fig. 1).

The maxilla removed 10 and 40 min after the application of ^{14}C-lidocaine (left) or ^{14}C-lidocaine with epinephrine (left) was frozen, and a 10 μm frontal section was sliced at the center of the site of drug application. The blackened area shows accumulation of ^{14}C-lidocaine. After 40 min, the blackened area increased in the maxillary section treated with lidocaine with epinephrine. In the maxillary section treated with lidocaine only, the blackened area almost disappeared.

Discussion

The addition of epinephrine delayed the time required for lidocaine concentration in the palatal mucosa and maxillary bone to reach the peak. The concentration of lidocaine in the mucosa peaked at around 10 min after application, although when epinephrine was added, it did not peak until 40 min. If the lidocaine concentration in the mucosa is correlated with its topical anesthetic effect, the addition of epinephrine extends the duration of this effect.

Conversely, the slower rate of increase in lidocaine concentration in the mucosa may delay the onset of its effect as a topical anesthetic. However, studies have found that an adequate anesthetic effect is achieved within 1–3 min of its application to the gingival mucosa.[20,21] In this study, the addition of epinephrine did not significantly affect lidocaine concentration up to 2 min after application. Therefore, we considered it unlikely that the addition of epinephrine delayed the onset of lidocaine's topical anesthetic effect.

With the addition of epinephrine, lidocaine still reached the maxillary bone after 40 min of application. The prolongation of the time for which lidocaine was localized in the mucosa may have increased the amount that penetrated the maxillary bone. This suggests that clinicians must wait sufficiently after application of epinephrine containing topical anesthetics before the initiation of invasive procedures, such as injection needle puncture and deciduous tooth extraction.

As the oral mucosa is rich in capillaries, topical anesthetics are rapidly absorbed into the bloodstream. Although no studies have been performed on the human oral mucosa, when lidocaine is sprayed on the upper airway mucosa, the concentration in blood reportedly peaks after 5–30 min.[22–25] This rapid rise of lidocaine concentration in blood is more likely to cause toxicity than a gradual rise.[10,26,27] In our study, the time required to reach the peak blood lidocaine concentration was increased from 20 min to 50 min after application due to the addition of epinephrine. This indicated that epinephrine inhibits the absorption of lidocaine into the bloodstream, thus lowering the rate at which the blood concentration rises. However, the peak concentration in the blood was higher when epinephrine was added. These findings warrant further studies to investigate the effect of epinephrine on the risk of local anesthetic toxicity. It has also been reported that it may affect the synthesis of methemoglobin, which occurs as a result of the metabolism of local anesthetics.[28]

Campbell *et al.*[10] and Adrian *et al.*[26] reported that the addition of epinephrine to the topical anesthetics neither prolonged the duration of anesthesia nor inhibited their absorption. Several other studies have reported that the anesthetic action of lidocaine applied to the mucosal surface peaks after 2–5 min, that epinephrine has low tissue permeability, and its addition to topical anesthetics has no effect on its duration of action.[7] As epinephrine is strongly polarized in aqueous solution, it is unable to pass through the cell membrane.[29] Since the cell membrane is composed of a lipid bilayer, it is more easily penetrated by fat-soluble substances, and as epinephrine is a water-soluble hormone with a receptor on the cell membrane surface, it has low fat solubility. This is considered to be the reason for its low tissue permeability.

The reasons for the difference between these reports and our results are unknown. However, it is possible that, when applied to the surface, epinephrine has no effect on the capillaries running through the deep mucosa but constricts the vessels running immediately beneath the mucosa to prolong the localization of lidocaine. This suggests that it may not be necessary for epinephrine to permeate the deep mucosa to inhibit the absorption of topical anesthetics into the bloodstream. We also accurately measured the lidocaine concentration in tissues using radioisotopes, whereas all previous reports were of clinical studies, and it is conceivable that epinephrine's effect may not be sufficient to affect the clinical action of anesthetics. As the addition of epinephrine delayed the increase in lidocaine concentration in the mucosa from 4 min after application, the possibility that previous studies may have measured its effect before the complete manifestation of its anesthetic action cannot be excluded.

This study has some limitations. We did not directly measure the anesthetic effect, nor did we investigate the suppression of toxicity or methemoglobinemia. Further clinical research to evaluate the anesthetic effect with epinephrine and animal studies to determine the decreasing effect for systemic toxicity of anesthetics and blood concentration of methemoglobin are required.

The results of this study demonstrated that epinephrine prolongs the localization of lidocaine applied to the oral mucosa and inhibits its absorption into the bloodstream. Therefore, further studies are required to investigate the clinical application of epinephrine-containing topical anesthetics on the oral mucosa. Use of epinephrine-containing topical anesthetics could make oral injections less painful and safer during dental procedures.

Declarations

Ethics approval and consent to participate

This study was approved by the Animal Experiment Committee of the Nippon Dental University School of Life Dentistry (approval No. 10-29).

All methods were carried out in accordance with the guidelines laid down by the revised Animals (Scientific Procedures) Act 1986 in the UK, Directive 2010/63/EU in Europe and ARRIVE (Animal Research: Reporting of in vivo Experiments).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during the current study are available in the Mendeley repository, Sunada K., Sasaki R. (2021). *Effect of Epinephrine on the Absorption of Lidocaine Following Application to the Oral Mucosa in Rats.* doi:10.17632/65pz7shjxy.1

Competing interests

The authors declare that they have no competing interests.

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Author contributions

KS: Conceptualization, Formal analysis, Supervision, Validation, Review & editing

RS: Data curation, Formal analysis, Investigation, Original draft writing

Both authors read and approved the final manuscript.

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References

1. Meechan JG. The use of EMLA for an intra-oral biopsy in a needle phobic: a case report. Anesth Prog. 2001;48:32–34.
2. Roller NW, Ship II. Lidocaine topical film strip for oral mucosal biopsies. J Oral Med. 1975;30:55–58.
3. Gangarosa LP. Iontophoresis for surface local anaesthesia. J Am Dent Assoc. 1974;88:125–128. doi:10.14219/jada.archive.1974.0038
4. Taware CP, Mazumdar S, Pendharkar M, MPharm, Adani MH, Devarajan PV. A bioadhesive delivery system as an alternative to infiltration anaesthesia. Oral Surg Oral Med Oral Path. 1997;84:609–615. doi:10.1016/S1079-2104(97)90360-7
5. Lee HS. Recent advances in topical anesthesia. J Dent Anesth Pain Med. 2016;16:237–244. doi:17245/jdapm.2016.16.4.237
6. Warren OU, Blackwood B. Acquired Methemoglobinemia. N Engl J Med. 2019;381:1158. doi:1056/nejmicm1816026
7. Catterall W, Mackie K. Local Anesthetics. In: Hardman JG, Limbird LE, editors-in-chief. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th ed. New York: McGraw-Hill Professional, 1996:341.
8. Adriani J, Zepernick R. Some recent studies on the clinical pharmacology of local anesthetics of practical significance. Ann Surg. 1963;158:666–671. doi:1097/00000658-196310000-00013

9. Löfström B. Aspects of the pharmacology of local anesthetic agents. Brit J Anaesth. 1970;42:194–206. doi:10.1093/bja/42.3.194
10. Campbell D, Adriani J. Absorption of local anesthetics. JAMA. 1958;168:873–877.
11. Pryor GJ, Kilpatrick WR, Opp DR. Local anesthesia in minor lacerations: topical TAC vs lidocaine infiltration. Ann Emerg Med. 1980;9:568–571. doi:10.1016/S0196-0644(80)80227-7
12. Smith SM, Barry RC. A comparison of three formulations of TAC (tetracaine, adrenaline, cocaine) for anesthesia of minor lacerations in children. Pediatric Emerg Care. 1990;6:266–270. doi:1097/00006565-199012000-00004
13. Ernst AA, Marvez-Valls E, Nick TG, Chin E, Wood E, Gonzaba WT. Lidocaine, adrenaline, tetracaine gel versus tetracaine, adrenaline, cocaine gel for topical anesthesia in linear scalp and facial lacerations in children aged 5 to 17 years. Pediatrics. 1995;95:255–258.
14. Ernst AA, Marvez-Valls E, Nick TG, Mills T, MinVielle L, Houry Det. Topical lidocaine adrenaline tetracaine (LAT Gel) versus injectable buffered lidocaine for local anesthesia in laceration repair. WJM. 1997;167:79–81.
15. Bush S. Is cocaine needed in topical anaesthesia? Ann Emerg Med. 2002;19:418–422. doi:10.1136/emj.19.5.418
16. Kravitz ND. The use of compound topical anesthetics: a review. J Am Dent Assoc. 2007;138:1333–1339. doi:10.14219/jada.archive.2007.0048
17. Vinci RJ, Fish SS. Efficacy of topical anesthesia in children. Arch Pediatr Adolesc Med. 1996;150:466–469. doi:10.1001/archpedi.1996.02170300020005
18. Akimoto T, Hashimoto S, Sunada K. Dexmedetomidine (12.5 lg/mL) improves tissue distribution, anesthetic action, and hemodynamic effects of lidocaine after palatal infiltration in rats. Odontology. 2016;104:390–396. doi:10.1007/s10266-015-0221-6
19. Hashimoto S, Yamashiro, Fujita K, Yasuda A, Sunada K. Effects of epinephrine on lidocaine pharmacokinetics and blood volume in the dental pulp. J Endod. 2014;40:1370–1374. doi:10.1016/j.joen.2014.02.029
20. Stern I, Giddon DB. Topical anesthesia for periodontal procedures. Anesth Prog. 1975;22:105–108.
21. Gill CJ, Orr II DL. A double blind crossover comparison of topical anesthetics. J Am Dent Assoc. 1979;98:213–214. doi:14219/jada.archive.1979.0476
22. Curran J, Hamilton C, Taylor T. Topical analgesia before tracheal intubation. Anaesthesia. 1975;30:765–768. doi:1111/j.1365-2044.1975.tb00952.x
23. Bromage PR. Concentrations of lignocaine in the blood after intravenous, intramuscular epidural and endotracheal administration. Anaesthesia. 1961;16:461–478. doi:10.1111/j.1365-2044.1961.tb13426.x
24. Scott DB, Littlewood DG, Covino BG, Drummond GB. Plasma lignocaine concentrations following endotracheal spraying with an aerosol. Br J Anaesth. 1976;48:899–902. doi:10.1093/bja/48.9.899

25. Viegas O, Stoelting RK. Lidocaine in arterial blood after laryngotracheal administration. Anesthesiology. 1975;43:491–493. doi:10.1097/00000542-197510000-00019
26. Adriani J, Campbell D Fatalities following topical application of local anesthetics to mucous membranes. JAMA. 1956;162:1527–1530. doi:10.1001/jama.1956.02970340017006
27. Scott DB. Evaluation of clinical tolerance of local anaesthetic agents. Brit J Anaesth. 1975;47:suppl 328–333.
28. Trapp L, Will J. Acquired Methemoglobinemia Revisited. Dent Clin N Am. 2010;54:665-675. doi:10.1016/j.cden.2010.06.007
29. Nakamura S, Matsuura N, Ichinohe T. A new method of topical anesthesia by using anesthetic solution in a patch. J Endod. 2013;39:1369–1373. doi:10.1016/j.joen.2013.07.019

Figures

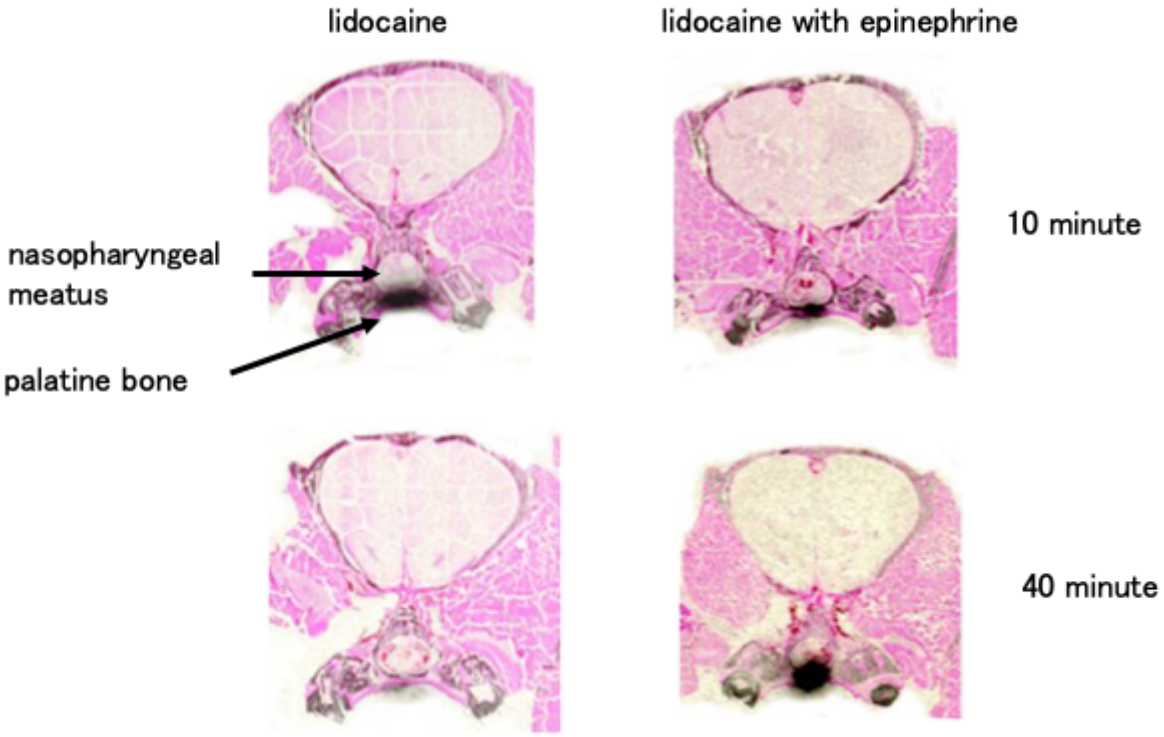

Figure 1

Autoradiograms of 14C-lidocaine in the coronary sections of maxilla The maxilla removed 10 and 40 min after the application of 14C-lidocaine (left) or 14C-lidocaine with epinephrine (left) was frozen, and a 10 μm frontal section was sliced at the center of the site of drug application. The blackened area shows accumulation of 14C-lidocaine. After 40 min, the blackened area increased in the maxillary section treated with lidocaine with epinephrine. In the maxillary section treated with lidocaine only, the blackened area almost disappeared.