

EFFECT OF β -ADRENORECEPTOR BLOCKADE WITH NADOLOL ON THE DURATION OF LOCAL ANESTHESIA

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ABSTRACT

Background. β -adrenoreceptor blockers, or β -blockers, are drugs commonly prescribed for hypertension, angina and migraine headaches. In a patient taking β -blocker medication, administration of a local anesthetic containing a vasoconstrictor could result in an adverse interaction.

Methods. The authors conducted a double-blind, randomized, crossover, placebo-controlled study to test the hypothesis that a nonselective β -blocker—nadolol—enhances vasoconstriction induced by the epinephrine contained in local anesthetic, thus resulting in an increased duration of anesthesia. Ten healthy male volunteers were given either a placebo or a single, standard oral dose of nadolol (80 milligrams). The upper lateral incisor teeth were anesthetized using lidocaine with or without epinephrine.

Results. The mean duration of pulpal and soft-tissue anesthesia was increased in subjects who took nadolol compared with those who took placebo by 17 minutes (58 percent) and 16.5 minutes (19 percent), respectively, when they received 1 milliliter of lido-

caine containing 1:100,000 epinephrine. These differences were both clinically and statistically significant ($P = .007$). Using lidocaine without epinephrine produced no clinically or statistically significant difference in duration of pulpal or soft-tissue anesthesia in the two groups of subjects. The authors noted no significant changes in blood pressure or pulse rate.

Conclusions. Administration of local anesthetic containing epinephrine to subjects receiving a β -blocker increased the duration of pulpal and soft-tissue anesthesia. There was no difference in duration of anesthesia between groups when local anesthetic without epinephrine was used.

Clinical Implications. Use of local anesthetic containing a vasoconstrictor should be avoided in patients taking β -blocker medication because of a possible adverse drug interaction. However, when a vasoconstrictor is indicated for hemostasis, the local anesthetic should be administered slowly and in small amounts as pulse rate and blood pressure are being monitored. The patient should be informed that the duration of anesthesia might be prolonged.

Drugs known as β -adrenoreceptor blockers, or β -blockers, are among the top 20 medications prescribed in the United States.¹ They commonly are used as part of the treatment regimen for hypertension, angina pectoris, subaortic stenosis and migraine headaches. β -blockers can be cardiac-selective, meaning that they preferentially block β_1 -adrenergic receptors in the heart, or nonselective, meaning that they act on both β_1 -adrenergic and β_2 -adrenergic receptors. Blocking β_1 -adrenergic receptors slows the heart rate, and blocking β_2 -adrenergic receptors causes arteriolar vasocon-

striction. Whereas the heart has primarily β_1 -adrenergic receptors, which are activated by neurally released catecholamines, it also has β_2 -adrenergic receptors which, although fewer in number, may interact with circulating epinephrine.² Also, it has long been known that adrenally released hormones can cause vasodilation in skeletal vascular beds.³ This vasodilation is mediated by β_2 -adrenergic receptors, which are accessible to both adrenally released and injected epinephrine.⁴

Epinephrine, a vasoconstrictor widely used in

dentistry, is contained in local anesthetics such as lidocaine, articaine, bupivacaine, etidocaine and prilocaine.^{5,6} Epinephrine acts directly on both α - and β -adrenergic receptors. Stimulation of α -adrenergic receptors located in blood vessels causes vasoconstriction, while stimulation of β -adrenergic receptors causes vasodilation. Responses to epinephrine are both site/receptor- and concentration-dependent. With low concentrations of epinephrine, the β -adrenergic effects predominate, producing vasodilation and increased heart rate. At higher concentrations of epinephrine, the α -adrenergic effects predominate, causing vasoconstriction and, in some cases, elevated blood pressure.⁷ The concentrations of epinephrine commonly used in dental local anesthetic (1:200,000 and 1:100,000) primarily induce local vasoconstriction, although an inadvertent generalized systemic response cannot be ruled out.⁸

Dental practitioners should be aware of the potential systemic and local effects of a β -blocker/vasoconstrictor interaction during the routine treatment of patients, as well as of the distinction between the actions of nonselective and cardiac-selective β -blockers. The cardiac-selective blockers do not interact with the vasodilating β_2 -adrenoreceptors. Thus, with the administration of epinephrine in the presence of cardiac-selective β_1 -blockade, unopposed vasoconstriction likely will not occur.

If, however, a patient is taking a nonselective β -blocker (such as nadolol or propranolol) when he or she receives local anesthetic with epinephrine,

the blockade of the β -receptor-mediated vasodilation effect may result in an unopposed α -receptor-mediated vasoconstriction.⁹ This can produce serious drug-induced (that is, iatrogenic) hypertension and could lead to cardiac arrest.¹⁰⁻¹² The amount of local anesthetic administered usually needs to be relatively large to produce this response, but one medical report cited such problems with an amount of epinephrine equivalent to as few as 3.6 dental cartridges of local anesthetic containing 1:100,000 epinephrine.¹³ If only a small amount of local anesthetic is used, as is the case in most dental procedures, a severe systemic reaction—although possible—is unlikely.¹⁴ At the injection site, however, increased vasoconstriction may result because of an unopposed α effect, which decreases the blood flow to the area and thereby prolongs anesthesia.

In light of these concerns, we undertook a study to investigate the effect of a single dose of nadolol, an orally administered nonselective β -blocker, on the duration of suprapariosteal local anesthesia in healthy human subjects. An *in vitro* study using the rat femoral artery demonstrated a significant increase in vasoconstriction when epinephrine and propranolol were combined.¹⁵ The hypothesis tested in this study is that the nonselective β -blocker nadolol enhances vasoconstriction induced by the epinephrine contained in local anesthetic, resulting in increased duration of anesthesia.

METHODS

We conducted this study as a double-blind, randomized,

crossover, placebo-controlled clinical trial. The “exposure” variable was the nonselective β -blocker drug nadolol, and the outcome variable was the duration of local anesthesia as measured in five-minute intervals.

After receiving approval from the internal review board of The University of Western Ontario, London, Ontario, Canada, we solicited 10 healthy male volunteers to participate in this clinical trial. The subjects who took part in the study were 20 to 40 years of age and had no history of high blood pressure or regular use of medication. Before being included in the study, each volunteer was required to complete a questionnaire that contained specific questions on asthma and cold- and exercise-induced wheezing. We excluded from the study any patients who had asthmatic symptoms, because the administration of a nonselective β -blocker such as nadolol could precipitate an asthmatic attack in these people. The volunteers signed a consent form.

One of the investigators (C.Z.) conducted a visual intraoral examination of each subject to establish that he had no periodontal problems, dental caries or existing restorations associated with the teeth we intended to study. Subjects were assigned randomly to test and control groups. Each subject received an oral dose of either nadolol (80 milligrams) or a placebo at approximately 11 a.m. Neither the study subjects nor the examiner was aware of the type of medication administered. Blood pressure and radial pulse rate were monitored automatically just before the medication or placebo was administered and at one, two

and three hours after administration.

At three hours, the operator anesthetized the upper left and right lateral incisors using either 1 milliliter of 2 percent lidocaine with 1:100,000 epinephrine or 1 mL of 2 percent lidocaine without epinephrine. The type of anesthetic used at each site was determined randomly and was unknown to both the subject and the operator. The operator retracted the subject's lip with his free hand to expose the tooth and the area to be anesthetized and to stretch the vestibular mucosa. After drying the mucosa, the operator inserted a short, 30-gauge needle at the greatest concavity of the mucobuccal fold and directed it toward the apex of the tooth. When bone was contacted, the operator withdrew the needle slightly to avoid injecting under the periosteum. After a negative aspiration, 1 mL of the anesthetic solution was slowly injected over a 20-second period. The operator then removed the needle and applied light finger pressure on the injected area for a few seconds to prevent any leaking of anesthetic solution or bleeding.

To assess pulpal anesthesia, the operator first isolated and dried the tooth. The electrode of a digital pulp tester (Model 2001, Analytic Technology) was coated with a viscous conductor paste and then placed on sound dried enamel in the middle third of the buccal surface of the tooth. To complete the electric circuit between the subject and the pulp tester, the subject grasped the metal portion of the pulp tester probe between his bare thumb and index finger while the dentist held the probe

in place on the tooth. The testing started with zero electric current flow, which was increased at a fixed rate such that a maximal reading would be achieved in 20 seconds. The subject was instructed to release the probe, thus breaking the circuit and establishing an immediate end-point reading for the pulp test, as soon as he began to feel a slight tingling or a sensation of heat or pain. The reading was repeated and the operator recorded the average of three consecutive readings.

To assess soft-tissue anesthesia, the operator exposed and dried the labial attached gingiva of the lateral incisor. He then pressed the tip of a dental explorer firmly into the middle third of the attached gingiva. He recorded the subject's response to the presence of pain. Pulpal anesthesia was defined as the absence of the subject's response to the maximal level of current of the pulp tester. Soft-tissue anesthesia was defined as the absence of the subject's response to a firm prick on the labial attached mucosa above the lateral incisor with a sharp explorer tip. Pulpal and soft-tissue anesthesia were assessed every five minutes after administration of the local anesthetic until pain was once again elicited. The duration of pulpal and soft-tissue anesthesia was recorded to the last five-minute interval at which anesthesia was present. Blood pressure and pulse rate were measured every 30 minutes until full recovery from the local anesthesia and then once again immediately before the subject was dismissed.

After a "wash-out" period of at least seven days, the subjects who previously had received

placebo were given nadolol, and those who previously had received nadolol received placebo. The experiment was repeated using identical methods and materials.

The difference in duration of anesthesia was tested for statistical significance using a paired *t*-test. We conducted an analysis of covariance (using SYSTAT, version 5.2.1, SPSS Inc.) to determine whether the observed difference in duration between types of anesthetic was related to the drug factor, the order of administration, or both. Age and body weight were used as covariables.

RESULTS

When the subjects received nadolol, the mean duration of pulpal anesthesia with epinephrine was longer compared with the control drug in all but two subjects. One subject experienced a slight reduction in duration of local anesthesia and one experienced no change. The duration of pulpal anesthesia with 1:100,000 epinephrine was 46.5 ± 14.3 (mean \pm standard deviation) minutes in the nadolol group while in the placebo group the mean duration of pulpal anesthesia was 29.5 ± 6.0 minutes. The observed mean difference in duration of pulpal anesthesia of 17.0 minutes (58 percent) was statistically significant ($P = .007$) (Table 1).

When local anesthetic without epinephrine was used, three subjects taking nadolol experienced an increase in duration of pulpal anesthesia compared with subjects taking the control drug, four subjects experienced no difference and three subjects experienced a comparative

TABLE 1

DURATION (IN MINUTES) OF DENTAL PULPAL ANESTHESIA.				
SUBJECT	ANESTHETIC WITH EPINEPHRINE		ANESTHETIC WITHOUT EPINEPHRINE	
	Received Placebo (Control)	Received Nadolol (Test)	Received Placebo (Control)	Received Nadolol (Test)
1	35	45	5	5
2	25	60	5	5
3	30	25	0	15
4	40	50	15	10
5	20	30	10	15
6	35	55	15	5
7	30	50	0	5
8	25	70	10	10
9	30	30	0	0
10	25	50	0	10
N	10	10	10	10
Mean	29.5	46.5	6.0	8.0
SD*	6.0	14.3	6.1	4.8

* SD: Standard deviation.

decrease in duration of anesthesia. The mean duration of pulpal anesthesia without epinephrine was 8.0 ± 4.8 minutes for the nadolol group, while the placebo group had a mean duration of pulpal anesthesia of 6.0 ± 6.1 minutes. This difference was not statistically significant (Table 1).

In the group that received nadolol, the mean duration of soft-tissue anesthesia with local anesthetic containing 1:100,000 epinephrine was 103.5 ± 12.7 minutes; among members of the group that received placebo, the duration was 87.0 ± 13.8 minutes. Nadolol increased the mean duration of soft-tissue anesthesia by 16.5 minutes (19 percent), which was statistically significant ($P = .007$). The mean duration of soft-tissue anesthesia without epinephrine was

16.0 ± 7.0 minutes for the group that received nadolol and 15.0 ± 10.0 minutes for the group that received placebo. There was no statistically significant difference observed in the mean duration of local anesthesia between these two groups (Table 2).

The analysis of covariance revealed no statistically significant difference among the order in which the drugs were administered, age, weight or drug-order interaction. However, a significant drug effect ($P = .015$) did occur that increased duration of pulpal anesthesia when local anesthetic with epinephrine was used.

There was a tendency toward a slowing of the pulse rate after the administration of both nadolol and placebo or after the administration of a local anes-

thetic with epinephrine (Figure 1). Systolic and diastolic blood pressures were lowered slightly in the group that received nadolol compared with the group that received placebo, and the administration of local anesthetic increased this effect slightly (Figure 2). We observed no statistically or clinically significant differences for pulse rate or blood pressure.

The majority of subjects reported no side effects; however, two subjects complained of feeling tired or "sluggish" after oral administration of nadolol. One subject complained of the same symptoms after the administration of placebo. Two subjects complained of "sore gums" at the probing site on the gingiva, but this sensation disappeared the day after the experiment.

TABLE 2

DURATION (IN MINUTES) OF SOFT-TISSUE ANESTHESIA.				
SUBJECT	ANESTHETIC WITH EPINEPHRINE		ANESTHETIC WITHOUT EPINEPHRINE	
	Received Placebo (Control)	Received Nadolol (Test)	Received Placebo (Control)	Received Nadolol (Test)
1	80	80	5	10
2	85	120	15	30
3	75	100	10	15
4	110	100	35	10
5	100	110	15	15
6	80	105	30	10
7	75	110	10	25
8	105	110	15	10
9	70	85	10	15
10	90	115	5	20
N	10	10	10	10
Mean	87.0	103.5	15.0	16.0
SD*	13.8	12.7	10.0	7.0

* SD: Standard deviation.

DISCUSSION

In this study, we investigated the interaction between a single exposure to 80 mg of the nonselective β -blocker nadolol and the suprapariosteal injection of 1 mL of the local dental anesthetic 2 percent lidocaine, with and without 1:100,000 epinephrine. We used nadolol for this study because it is a commonly used oral, nonselective β -blocker. Nadolol is not metabolized in the liver after oral administration but is primarily eliminated in urine and feces.¹⁶ Therefore, the blood concentration of nadolol is quite predictable. After a single 80-mg oral dose of nadolol, the blood concentration of nadolol reaches a peak in three hours with a half-life of 15 hours.¹⁷

We administered the local

anesthetic three hours after administration of the oral dose of nadolol to take advantage of peak blood levels. Published studies have shown that the peak blood levels of nadolol in patients regularly taking 80 mg of the drug per day were similar to the blood levels we observed in our subjects after they received a single dose of 80 mg.^{18,19} Therefore, a comparable therapeutic effect was produced.^{18,19}

However, it should be pointed out that this single-dose study should not be directly extrapolated to a clinical situation of long-term therapy. The single-dose administration of a β -blocker, as we used experimentally in this study, produces pharmacological effects that are significantly different from those associated with long-term

administration. Nonselective β -blockers given in single doses are associated with bradycardia, decreased cardiac output and an increase in peripheral vascular resistance. As described in this article, these effects result from a blockade of both β_1 - and β_2 -receptors. However, with long-term administration, the heart rate and cardiac output effects become less prominent, and a decrease in peripheral vascular resistance occurs.²⁰ This later effect is thought to be attributable to the inhibition of renin release and subsequent activation of the angiotensin-aldosterone system. However, considering the numerous reports that an acute hypertensive response still happens in patients taking nonselective β -blockers over the long term

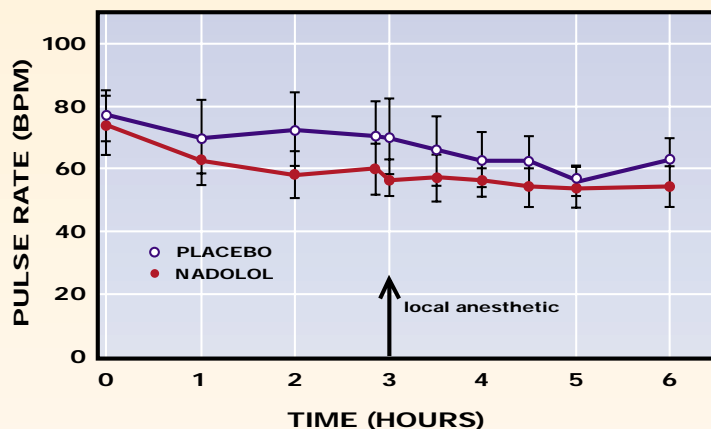


Figure 1. The effect of nadolol and local anesthetic with epinephrine on the subjects' pulse rates (shown in beats per minute, or BPM, over time, shown in hours).

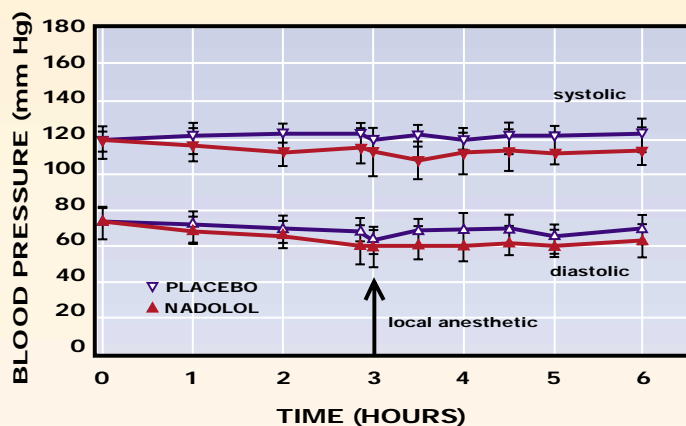


Figure 2. The effect of nadolol and local anesthetic with epinephrine on the subjects' blood pressure (shown in millimeters of mercury, or mm Hg, over time, shown in hours).

when they receive epinephrine, we make the assumption that the blood vessels are still responsive in these patients.

After a single oral dose of nadolol, the durations of both pulpal and soft-tissue anesthesia were significantly increased. This effect can be attributed to enhanced local vasoconstriction resulting from the nadolol/epinephrine interac-

tion. The basis of this interaction is epinephrine's ability to act on both α - and β -adrenergic receptors. In the presence of a nonselective β -blocker, the α effect is unopposed and results in enhanced vasoconstriction with prolongation of the local anesthetic effect.⁹ The small amount of epinephrine used in this study did not cause any significant change in blood pres-

sure or heart rate. However, more sensitive tests may detect changes in cardiovascular function such as peripheral vascular resistance, cardiac output and myocardial relaxation time.

An increased duration of pulpal anesthesia is not necessarily synonymous with decreased pulpal blood flow. However, it is theoretically possible that prolonged vasoconstriction, which may cause ischemic damage to the dental pulp and soft tissue, may occur. We did not measure this in our study, and we noted no clinical signs or symptoms of soft-tissue or pulpal necrosis. It would appear that pulp and soft-tissue ischemia due to a possibly longer duration of vasoconstriction does not present a problem in healthy subjects, but hypertensive patients with already compromised blood vessels and perfusion may be at greater risk of developing local ischemia.

It is well-known that β -receptors are sparsely distributed in skin and oral mucous membranes. However, β_2 -receptors are present in blood vessels that supply skeletal muscles, connective tissue and facial veins.^{7,8,21,22} In addition, α - and β -adrenergic receptors have been demonstrated in dental pulp, although not consistently.^{23,24} The epinephrine injected with a local dental anesthetic probably is acting on these receptors, and this is where the drug/drug interaction takes place.

To prevent or minimize both systemic and local drug/drug interactions in patients taking a nonselective β -blocker and receiving a local anesthetic, dentists should consider several management strategies (Table 3). The preferred strategy is to avoid using a local anesthetic

TABLE 3

MANAGEMENT STRATEGIES FOR PATIENTS TAKING NONSELECTIVE β -BLOCKERS.	
STRATEGY	RECOMMENDATION
Use a local anesthetic without vasoconstrictor (such as 4 percent prilocaine, 3 percent mepivacaine)	Recommended and preferred if hemostasis is not a concern
Use a local anesthetic with a lower concentration of epinephrine (for example, 4 percent prilocaine with 1:200,000 epinephrine)	Recommended if available
Use the minimum amount of local anesthetic containing 1:100,000 epinephrine <ul style="list-style-type: none"> — Administer the local anesthetic in increments of one-half to one cartridge — Monitor the patient's blood pressure and pulse — Repeat if additional increments are necessary — Inform the patient of possible longer duration of anesthesia 	Recommended
Use a local anesthetic with another vasoconstrictor (such as levonordefrin, norepinephrine, phenylephrine)	Not recommended
Alter the β -blocker medication <ul style="list-style-type: none"> — Discontinue use of the nonselective β-blocker — Change to a cardioselective β-blocker 	Not recommended

that contains a vasoconstrictor. This is a good option if adequate local anesthesia is achieved and hemostasis is not a concern. Although lidocaine without a vasoconstrictor is capable of producing a short duration of pulpal anesthesia by supra-periosteal injection, other local anesthetics—such as 4 percent prilocaine and 3 percent mepivacaine—can provide longer periods of anesthesia.⁷

If a vasoconstrictor in the local anesthetic is desirable for hemorrhage control, there are several options. The patient's physician could be consulted about whether use of the β -blocker could be temporarily discontinued before the dental procedure. However, this is unacceptable because of the possibility of a withdrawal-rebound syndrome, which can have serious consequences.²⁵⁻²⁸ Instead, where clinically appropriate, a cardiac-selective β -

blocker can be used to replace the nonselective β -blocker, because the more selective the β -blocker, the less chance that the interaction with epinephrine will occur. However, this decision should be made only by the patient's physician and may occur at a time inconvenient to the dental treatment.

A second option is using a local anesthetic containing a vasoconstrictor other than epinephrine. Levonordefrin (1:20,000) is available with 2 percent mepivacaine. Levonordefrin is primarily an α -agonist with weak β -receptor stimulation. Therefore, the chance of its producing an interaction with a nonselective β -blocker is reduced. However, a hypertensive response to levonordefrin in a patient receiving propranolol has been reported.²⁹ More studies are needed to investigate the effect of other "purer" vasoconstrictors, such as

phenylephrine and norepinephrine, in local anesthetics before they can be recommended for use in this patient population.

If a dentist chooses to use epinephrine in the local anesthetic solution, the patient should be informed of the possibility that the duration of anesthesia will be longer than that normally expected. When administering the local anesthetic, the dentist should follow a protocol that minimizes any potential for complications. Initially, he or she should administer—slowly—a small amount of local anesthetic, such as one-half cartridge with 1:100,000 epinephrine. He or she should assess the patient's blood pressure and pulse rate before administering the local anesthetic and again three to five minutes later.^{7,25} The dentist should repeat this protocol for each subsequent administration of local anesthetic to identify a

potential hypertensive response.

The maximum dose of epinephrine administered in local anesthetic for patients taking a nonselective β -blocker should not exceed 3 micrograms per kilogram every 30 minutes.³⁰ This represents 150 μg for a patient weighing 50 kg, or the equivalent of eight cartridges of local anesthetic containing 1:100,000 epinephrine. This dose might be appropriate for a patient treated in an environment with cardiovascular monitoring and support, but it is risky for a patient treated in the typical dental office. The dose of epinephrine in local anesthetic should be kept as low as possible in patients who are taking nonselective β -blockers.

CONCLUSION

The administration of local anesthetic containing epinephrine to subjects receiving a β -blocker—nadolol, in this case—increases the duration of pulpal and soft-tissue anesthesia. This can be attributed to enhanced local vasoconstriction resulting from the nadolol/epinephrine interaction. There was no difference in duration of anesthesia between test and control groups when local anesthetic without epinephrine was used. We observed no significant changes in blood pressure or pulse rate with the low dose of epinephrine used in this study; however, more sensitive tests may detect a systemic effect. ■

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