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Local Anesthetics

Is There an Advantage to Mixing Solutions?

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The advantages to using a 50/50 mixture of lidocaine and bupivacaine with respect to onset and duration of local anesthesia instead of using the solutions independently were evaluated. In a double-blind randomized experiment, 12 subjects, each volunteering both feet, were studied. One foot was injected with 1 ml of one of the following three solutions: 1% plain lidocaine, 0.25% plain bupivacaine (Marcaine®[1]), or a 50/50 mixture of 1% lidocaine and 0.25% bupivacaine; and in the other foot, a 1-ml injection of normal saline as a blinded control. A 5.07 (10 g) Semmes-Weinstein monofilament wire was used for testing for sensory blockade, and the onset and duration of anesthesia was recorded for each subject. It was determined that there was no significant difference in the mean onset times for the three solutions, and no significant difference between the durations of anesthesia of plain lidocaine and the 50/50 mixture. Additionally, it was determined that bupivacaine had a prolonged duration of anesthesia compared with the other two solutions. The results of this preliminary study suggest that there is no clinical advantage, with respect to onset and duration of local blockade, to using a 50/50 mixture of plain lidocaine and plain bupivacaine in place of their independent use.

In a preliminary survey of physicians at a recent scientific seminar, 52.4% stated that they use a 50/50 mixture of lidocaine and bupivacaine for local anesthesia prior to bunion surgery, and 47.6% stated that they use them independently of one another. What then is the determining factor for choice? What is the clinical evidence suggesting that one has merit over the other? This study attempts to objectively determine whether there is a clinical advantage to mixing solutions, or, if in fact, the combination of local anesthetics has no benefit, or is even counterproductive to using them independently.

Local anesthetics are drugs that reversibly inhibit the propagation of impulses along the nerve fiber of a peripheral nerve. The cellular unit of a peripheral nerve is called the neuron. A neuron consists of a cell body and a long process called the nerve fiber. In a typical peripheral nerve, the nerve fibers are bundled together into fascicles, which are, in turn, grouped together to form the nerve trunk. The fibers, fascicles, and trunk are surrounded and supported by connective tissues, commonly known as the epineurium, perineurium, and endoneurium. The site of action of local anesthetics is the neuronal membrane, which is a phospholipid bilayer interspersed with

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®[1]Astra USA, Inc, Westboro, MA.

negatively charged protein molecules, to which it is impermeable. It is the electronegativity of these intracellular proteins that imparts its negative resting membrane potential of -90mV to the nerve fiber.[1]

On excitation of nerve fibers, positively charged sodium ions, to which the lipid membrane is impermeable, enter the cells through specific channels and alter the electric potential. When the transmembrane potential reaches its threshold value, -50mV, sodium channels become wide open, and the sudden influx of positive ions causes the membrane potential to rise rapidly to +30mV. This is known as depolarization. Once depolarization has ended, sodium channels close and there is an efflux of positively charged potassium ions, which are freely permeable. This process restores the resting membrane potential and is known as repolarization. The wave of depolarization and repolarization is what transmits an impulse along a nerve fiber.[1]

Lidocaine and bupivacaine are amide type of local anesthetics, which means their chemical structure is such that they have an amide linkage between the aromatic nucleus and the amino or piperidine group.[1, 2] Lidocaine is a lipophilic compound that exists as a weak base with a pKa (measure of acid strength) of 7.86, a half-life of 1.6 hr, and is 64% bound to plasma protein.[2] Bupivacaine is also a lipophilic, weakly basic compound, but its pKa is 8.05, its half-life is 2.7 hr, and is 84% to 95% bound to plasma protein.[2] The onset of action for lidocaine plain solution for peripheral nerve block is rapid, ranging from 1 to 3 min, with the duration of action lasting 1 or 2 hr or more.[1-3] Bupivacaine exhibits a slower onset of anesthesia, ranging from 2 to 10 min, but is generally known to have a longer duration of action.[3] The duration of peripheral nerve blocks produced by bupivacaine may last up to 7 hr.[2] For peripheral nerve block, lidocaine is commonly used as a 1% or 2% solution, with or without epinephrine, and bupivacaine is commonly used as a 0.25% or 0.5% solution, with or without epinephrine (Table 1).

The rate of onset of a local anesthetic is largely determined by its pKa, that is, the pH at which 50% of the drug exists in its active, ionized form. Local anesthetics are weak bases, and thus when injected, those with a pKa near physiologic pH (approximately 7.0) will be less ionized than those with a higher pKa. Solutions with lower pKa constants will diffuse more readily through tissues and neuronal membranes, providing a more rapid onset. Although the exact mechanism of action of local anesthetics is still a topic of debate, it is hypothesized that local anesthetic molecules bind to receptors in the sodium channels, thus blocking the influx of sodium ions, depolarization, and subsequent impulse conduction.[1]

Local anesthetics such as lidocaine and bupivacaine are available most commonly as water-soluble hydrochloride salts. In an aqueous solution, they readily dissociate into their respective acidic and basic parts. The nonionized base is able to diffuse through tissue barriers, where it combines with a proton to form the activated acid when reaching the neuronal membrane. Since the pKa of lidocaine is less than that of bupivacaine, it will dissociate into its nonionized part more readily, and thus be able to cross lipid membranes more quickly and achieve a perceived more rapid effect. Conversely, the slower reported onset of bupivacaine can be explained by its higher relative pKa, meaning it will not as easily release its proton and will take longer to cross lipid membranes and exert its anesthetic effects.[1] Thus, it has been theorized that the potency of a local anesthetic is a function of its relative lipid solubility. The more lipid soluble a drug, the more readily it penetrates the neuronal membrane and reaches its site of action.[4]

Lidocaine and bupivacaine, like all amide anesthetics, are rapidly metabolized in the liver through conjugation with glucuronic acid. The majority (more than 90%) of these compounds are excreted by the kidney in the form of various metabolites, with less than 10% being excreted unchanged.[3] Because of the rapid rate of metabolism by the liver, any condition that affects liver function may alter the kinetics, and as such may lead to an increase in half-life.[3]

The rate of systemic absorption of local anesthetics is a function of many parameters. These include the route of administration, the total dose and concentration administered, the vascularity of the site of injection, and the presence or absence of epinephrine in the anesthetic solution.[1, 3]

A dilute concentration of a vasopressor such as

Table 1. Characteristics of Local Anesthetics

Local	Onset (min)	Duration (hr)	Half-life (hr)	pKa	Bound %
Lidocaine 1% or 2%	1 to 3	1 to 2	1.6	7.86	64
Bupivacaine 0.25% or 0.5%	2 to 10	7	2.7	8.05	84 to 95

epinephrine (1:200,000) reduces the rate of absorption and peak plasma concentration of the local anesthetic, and thus may prolong anesthesia. Although the addition of a local vasoconstrictor like epinephrine to lidocaine will potentiate the anesthetic effect, doing the same to bupivacaine, it is theorized, does little to increase duration of action therein.[1] In a recent study, Howe and Williams[5] concluded that when epinephrine is not contraindicated in patients, 2% lidocaine with epinephrine lasts almost as long as 0.5% bupivacaine plain.

According to Birke and Sims[6], Semmes-Weinstein monofilaments were found to be the most effective methods of measuring sensory deficits in the foot, and thus were used as the means of sensory testing in this study. The use of the Semmes-Weinstein monofilament wire as the standard for testing for pressure sensation can be attributed to the fact that the monofilaments have been standardized in their length and thickness.[7] Therefore, when applied to the skin, the amount of pressure administered to the patient is a function of the instrument and not the examiner.[7]

The purpose of this study is to examine what the potential effects of mixing the two solutions in equal parts may be on the onset and duration of anesthesia. Is there a benefit to a 50/50 mixture of lidocaine plain and bupivacaine plain over using them independently? In a study published in 1991, the authors concluded that for epidural anesthesia, the combination of bupivacaine and lidocaine offered no clinical advantage with respect to pain management over bupivacaine alone.[8] This study attempts to expand this research by incorporating lidocaine plain as a variable and also focusing on the onset and duration of local blockade as opposed to epidural.

Null Hypothesis

The use of a 50/50 mixture of lidocaine and bupivacaine for peripheral nerve blockade would result in the same onset and duration of anesthesia as the use of the products independently.

Methods

Twelve subjects, all male medical students, were selected based on relative similarities in age, weight, and overall body size for a double-blind, placebo-controlled study of local anesthetics. Each subject volunteered both lower extremities for the purpose of the study. Twelve hr before the study, using 18-gauge needles, 1-ml tuberculin syringes were loaded: 12 with 1 ml of normal saline, four with 1 ml of 1% lidocaine plain (10 mg), four with 1 ml of 0.25% bupivacaine plain (2.5 mg), and four with 1 ml of a 50/50 mixture of the two respective local anesthetic solutions.

Each syringe was numbered and labeled one through 24 by an independent party who kept the contents of each confidential. Each subject was automatically matched, by number, with one syringe containing the placebo and the other syringe receiving one of the test groups. The numbers of the respective syringes for each subject were then recorded on individual record time sheets. The master list of which subject received which solution was then sealed in an envelope by the independent party, and it remained unopened until the conclusion of the study.

The means of determining which foot was to receive the placebo was randomly determined in advance by the flip of a coin, and blinded from the investigator. A 30-gauge, 1-inch needle was used for the injections. Four subjects received an injection of 1 ml of 1% lidocaine plain in one foot, and 1 ml of normal saline, the experimental placebo, in the other foot. Four subjects received an injection of 1 ml of 0.25% bupivacaine plain in one foot, and 1 ml of normal saline in the other foot. Four subjects received a 50/50 mixture of 0.5 ml of 1% lidocaine plain and 0.5 ml of 0.25% bupivacaine in one foot, and the normal saline placebo in the other foot. The site of injection for the study was the first interspace on the dorsum of the foot, in the area of the deep peroneal nerve.

All of the injections were given by the same researcher, who again was unaware of what was being given. Each subject area was prepped with alcohol, and then 1 ml was injected into the first interspace of one foot, until 1 ml was infused. Each subject was instructed on the proper use of the monofilament wire and a demonstration was given by the researcher in advance. The injection of local anesthetic penetrated the epidermis, dermis, and subcutaneous tissue, and thus affected the encapsulated nerve endings therein, namely pacinian and Meissner's corpuscles. Pacinian corpuscles are the largest of the encapsulated receptors, and are responsible for pressure sensation, whereas Meissner's corpuscles are receptors of touch sensitivity.[9] The infiltration of local anesthetic in the first interspace was intended to act on these receptors, thus altering both pressure and touch sensation.

As soon as the injection began, the researcher started a timer, and at 15-sec intervals for the first 2 min, and then each minute thereafter, used the 10-g, 5.07 Semmes-Weinstein monofilament wire to determine whether full sensation was present or loss of sensation had been achieved. If loss of sensation was

achieved within the first 10 min, then the researcher recorded the onset time on the record sheet, and proceeded to inject the contralateral limb. If after 10 min, however, no loss was reported by the subject, the researcher assumed this was the control foot, and injected the other foot. Following the onset of action of the anesthetic, the researcher continued to test the subject personally until 10 min had elapsed, and then each subject was responsible for self-testing until the end of the study. The study concluded when the subject felt the same sensations in both interspaces, thus clinically determining that anesthesia had ceased. Meanwhile, each subject recorded on the record sheet whether sensation was present or absent, in each foot, at 15, 25, 40, and 60 min after the injection, and then every 60 min thereafter until the sensation returned.

The record sheets were then returned to the researcher and onset and duration times were tabulated for each subject, and the following statistical analyses were made.

Data Analysis

It was assumed all onset and duration values were drawn randomly from a population of gaussian-distributed (bell-shaped) values. Individual onset and duration values were used to compute mean onset (in seconds) and mean duration (in minutes); these values were also used in a one-way analysis of variance (ANOVA) to compare treatment means. The ANOVA tested the hypothesis that there were no significant differences among population means:

$$H_0: \mu_L = \mu_B = \mu_{L+B}$$

Levene's test was performed to determine whether the assumption of homogeneity of variances was valid.[10] Decisions on all statistical tests used the $\alpha = 0.05$ level of significance.

Results

Analysis of Variance for Treatment Means

Levene's test indicated that there was validity for the assumption of homogeneity of sample variances for both onset (LE. = 0.11, probability = 0.89) and duration (LE. = 1.08, probability = 0.38), and so ANOVA was appropriate for the comparison of treatment means. The results of the ANOVA are shown in Figure 1 and Table 2. Mean onset in all three treatments occurred approximately within 80 to 100 sec. There were no significant differences among sample means for onset (probability = 0.63); On the other hand, there were significant differences among treatment means for duration (probability = 0.02): mean duration for lidocaine alone and the lidocaine and bupivacaine mixture were approximately 3.5 hr (no significant difference), but mean duration for bupivacaine alone was approximately 9 hr, a statistically significant difference (Table 3).

Discussion

Are both the rapid onset and long duration achieved by mixing lidocaine and bupivacaine in equal parts? If so, then why? Is it that the lower pKa of lidocaine

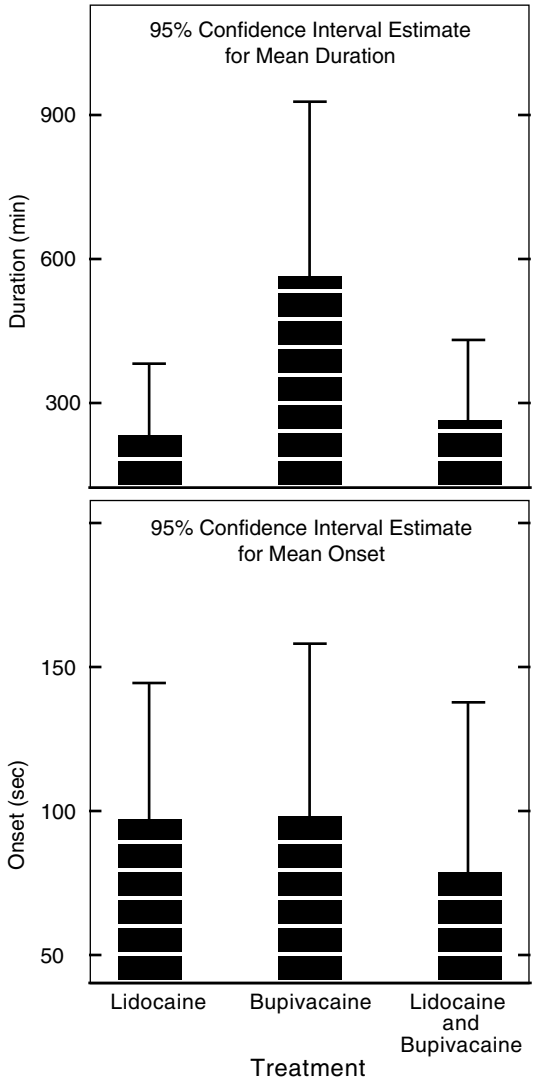

Figure 1. Mean onset and mean duration values per treatment. Vertical extension equals 95% confidence interval estimate (upper range) for sample mean (1-ml 1% lidocaine only, 1-ml 0.25% bupivacaine only, 0.5-ml 1% lidocaine and 0.5-ml 0.25% bupivacaine).

Table 2. ANOVA for Mean Onset and Mean Duration

Variable	Source	DF	Mean Square	F-Ratio	Probability Null Hypothesis is True
Onset	Between	2	475	0.49	0.63
	Within	9	978.5		
	Total	11			
Duration	Between	2	169,258	6.64	0.02
	Within	9	25,508		
	Total	11			

Table 3. Mean Onset and Duration Times

Solutions	Mean Onset (sec)	Mean Duration (hr)
Lidocaine 1%	98.8	3.17
50%/50% (Lidocaine, bupivacaine)	81.3	3.75
Bupivacaine	101.3	9.38

has the benefit of early onset and the higher pKa of bupivacaine allows it to essentially bind the receptors for a longer period of time, thus increasing the duration of its action? An extensive literature search revealed that there previously has not been a study asking whether there is an advantage to mixing solutions in achieving peripheral anesthesia.

For many years, physicians and surgeons have discussed the advantages of their choice of local anesthetic, citing literature based on chemical theories to support their views. This study is the first to compare the most common combinations in a randomized double-blinded manner.

The results of this preliminary study indicate that with respect to onset and duration of anesthesia, there is no significant advantage to using a 50/50 mixture compared with using the two solutions independently. The use of the mixture did not prove to have the advantage of early onset and prolonged duration, as was hypothesized. In fact, the onset and duration of the mixture appeared to be similar to that of lidocaine plain; thus asking the question, why mix the solutions at all?

Conclusion

The findings indicate that there was no significant difference in onset times for the three solutions, and that if prolonged duration is warranted, then bupivacaine is the obvious choice, lasting many hours longer than either of the other two solutions. Since the results suggest that there is not a significantly longer onset of anesthesia when using plain bupivacaine over plain lidocaine, why use lidocaine at all in adults when long-term anesthesia is desired? This preliminary investigation opens the door for more extensive research, as local anesthetic blocks are, by far, the most common choice for inducing peripheral anesthesia.

References

1. CHUNG D, LAM A: "Local Anesthetics," in *Essentials of Anesthesiology*, 2nd Ed, WB Saunders, Philadelphia, 1990.
2. SWINYARD E: "Local Anesthetics," in *Remington's Pharmaceutical Sciences*, 17th Ed, ed by AR Genarro, Mack Publishing, Easton, PA, 1985.
3. ARKY R: *Physicians' Desk Reference*, 50th Ed, Medical Economics, Montvale, NJ, 1996.
4. CHUNG D, LAM A: "Intravenous Anesthetics," in *Essentials of Anesthesiology*, 2nd Ed, WB Saunders, Philadelphia, 1990.
5. HOWE NR, WILLIAMS JM: Pain of injection and duration of anesthesia for intradermal infiltration of lidocaine, bupivacaine and etidocaine. J Dermatol Surg Oncol **20:** 459, 1994.
6. BIRKE JA, SIMS DS: Plantar sensory threshold in the Hansen's disease ulcerative foot. Presented at the Proceedings of the International Conference on Biomechanics and Clinical Kinesiology of Hand and Foot; December 16-18, 1985; Madras, India.
7. OLMOS P, CATALAND S, O'DORISIO T, ET AL: The Semmes-Weinstein monofilament as a potential predictor of foot ulceration in patients with noninsulin-dependent diabetes. Am J Med Sci **309:** 76, 1995.
8. SINATRA RS, GOLDSTEIN R, SEVARINO FB: The clinical effectiveness of epidural bupivacaine, bupivacaine with lidocaine, and bupivacaine with fentanyl for labor analgesia. J Clin Anesth **3:** 219, 1991.
9. CORMACK DH: "The Integumentary System," in *Essential Histology*, JB Lippincott, Philadelphia, 1993.
10. SOKAL RR, ROHLF FJ: "Assumptions of Analysis of Variance," in *Biometry*, 3rd Ed, WH Freeman, New York, 1995.