



THE JOURNAL OF THE AMERICAN DENTAL ASSOCIATION



## The use of compound topical anesthetics: A review

Neal D. Kravitz

*J Am Dent Assoc* 2007;138;1333-1339

---

*The following resources related to this article are available online at [jada.ada.org](http://jada.ada.org) ( this information is current as of November 23, 2009 ):*

**Updated information and services** including high-resolution figures, can be found in the online version of this article at:

<http://jada.ada.org/cgi/content/full/138/10/1333>

This article appears in the following **subject collections**:

Dental Equipment/Instruments

[http://jada.ada.org/cgi/collection/dental\\_equipment\\_instruments](http://jada.ada.org/cgi/collection/dental_equipment_instruments)

Information about obtaining **reprints** of this article or about permission to reproduce this article in whole or in part can be found at:

<http://www.ada.org/prof/resources/pubs/jada/permissions.asp>

# The use of compound topical anesthetics

## A review

Neal D. Kravitz, DMD, MS

Compounding is the process by which the pharmacist or doctor combines, mixes or alters pharmaceuticals or ingredients to create a custom-made medication in accordance with a prescription.<sup>1</sup> Pharmaceutical compounds in the form of anti-inflammatories, mouthrinses, toothpastes, antibiotic preparations, soaps, electrolyte troches, bleaching gels and strong topical anesthetics are commonplace in dentistry. In particular, compound topical anesthetics are applied to patients by pediatric dentists for restorative procedures, by periodontists for scaling and root planing procedures, by orthodontists for soft-tissue laser surgery and placement of orthodontic temporary anchorage devices (TADs), and by oral surgeons for facial rejuvenating procedures. In 2006, however, several U.S. Food and Drug Administration (FDA) advisory reports were issued regarding the potential hazards of using compound topical anesthetics.

In January 2007, I conducted a search on PubMed to identify English-language, full-text articles published from Jan. 1, 1980, through Dec. 31, 2006. The search terms I used were “topical,” “anesthetic,” “compound,” “pharmaceutical” and “Food Drug Administration.” I also searched for relevant

## ABSTRACT



**Background.** The author reviewed the history of, federal regulations regarding, risks of and adverse drug reactions of five compound topical anesthetics: tetracaine, adrenaline/epinephrine and cocaine (TAC); lidocaine, adrenaline/epinephrine and tetracaine (LET); lidocaine, tetracaine and phenylephrine (TAC 20 percent Alternate); lidocaine, prilocaine and tetracaine (Profound); and lidocaine, prilocaine, tetracaine and phenylephrine with thickeners (Profound PET).

**Types of Studies Reviewed.** The author reviewed clinical trials, case reports, descriptive articles, and U.S. Food and Drug Administration (FDA) regulations and recent public advisory warnings regarding the federal approval of and risks associated with the use of compound topical anesthetics.

**Results.** Compound topical anesthetics are neither FDA-regulated nor -unregulated. Some compounding pharmacies bypass the new FDA drug approval process, which is based on reliable scientific data and ensures that a marketed drug is safe, effective, properly manufactured and accurately labeled. Two deaths have been attributed to the lay use of compound topical anesthetics. In response, the FDA has announced the strengthening of its efforts against unapproved drug products.

**Clinical Implications.** Compound topical anesthetics may be an effective alternative to local infiltration for some minimally invasive dental procedures; however, legitimate concerns exist in regard to their safety. Until they become federally regulated, compound topical anesthetics remain unapproved drug products whose benefits may not outweigh their risks for dental patients.

**Key Words.** Topical anesthetics; U.S. Food and Drug Administration; compounding.

*JADA 2007;138(10):1333-9.*

Dr. Kravitz was an orthodontic resident, Department of Orthodontics, University of Illinois at Chicago College of Dentistry, when this article was written. He now is in private practice in Chantilly, Va. Address reprint requests to Dr. Kravitz at 6017 Makely Drive, Fairfax Station, Va. 22039, e-mail "info@kravitzorthodontics.com".

articles, using the reference lists of already identified articles.

In this article, I review the history, regulations, recent FDA warnings and life-threatening side effects of compound topical anesthetics. I examine clinical trials, case reports, descriptive articles, FDA regulations and recent public advisory warnings regarding the federal approval and risks associated with the use of compound topical anesthetics.

## PHARMACEUTICAL COMPOUNDING

Pharmaceutical compounding has been part of pharmacy practice since its origins. Before synthetic and premade pharmaceuticals were available, physicians would write prescriptions that local pharmacists would compound to produce capsules, tablets or suspensions. Industrial drug manufacturing, however, was able to produce drugs more efficiently and in bulk quantities. This led to the decline in compounding at local pharmacies, which could not compete on the same scale. Today, there has been a re-emergence of larger, multicenter compounding pharmacies that provide hundreds of custom-made medical, dental and veterinary medications.

Pharmaceutical compounding is not the same as drug manufacturing. Drug manufacturing is defined as the production, preparation, propagation, processing and packaging of a device or labeling of the commercial container.<sup>2</sup> Unlike customized compound pharmaceuticals, manufactured drug products are mass-produced and federally regulated under the Federal Food Drug and Cosmetic Act.

**FDA approval of pharmaceutical compounds.** Through the early 20th century, several worthless and often deadly elixirs were being mass-produced and distributed throughout the United States. The Elixir Sulfanilamide incident, in which more than 100 people died after taking a legal, but toxic, drug in 1937, prompted President Franklin Delano Roosevelt to sign the Food, Drug, and Cosmetic Act on June 25, 1938 (Table 1). This act brought cosmetic and medical devices under federal control. However, the 1938 act was aimed at regulating industrial manufacturers, not the neighborhood compounding pharmacy, which allowed compounding to continue as a normal function of the profession for almost 60 years.

The Food and Drug Administration Modernization Act (FDAMA) of 1997 attempted to clarify

the status of pharmacy compounding under federal law.<sup>3</sup> Under section 503A of the FDAMA, drug products that are compounded on a customized basis are exempt from the FDA's new drug approval requirements, under the provision that the provider does not advertise these products to the public.<sup>2</sup> In 2002, the U.S. Supreme Court ruling in *Thompson, Secretary of Health and Human Services, et al., v. Western States Medical Center, et al.*, invalidated the provisions of section 503A under constitutional violation of commercial free speech. Today, drug products compounded at pharmacies are neither FDA-regulated nor -unregulated (Table 1).<sup>4</sup>

**Abuse and violation of FDA policy.** Many large compounding pharmacies have sought shelter under this murky federal status, and their practices are more consistent with those of drug manufacturers.<sup>5</sup> For example, some of these large compounding pharmacies routinely produce bulk quantities of compound pharmaceuticals before receiving a prescription. According to the law, however, compounding may be done only for the needs of individual patients.<sup>4</sup>

To date, the FDA defers to state authorities regarding violations of FDAMA related to pharmacy compounding. For significant violations of 21 USC §351 (adulterated drugs and devices); §352 (misbranded drugs and devices) and §355 (new drugs) of FDAMA, the FDA may initiate regulatory action with seizure, injunction, prosecution or a combination thereof.

**Recent FDA warning regarding patients' use of compound topical anesthetics.** On Dec. 5, 2006, the FDA issued a public health advisory alert about the potential life-threatening side effects of compound topical anesthetics.<sup>6</sup> Exposure to high concentrations of local anesthetics can lead to serious adverse reactions, including anesthetic overdose, seizures, irregular heartbeats and death. The FDA issued warnings to five firms—Triangle Compounding Pharmacy (Cary, N.C.), University Pharmacy (Salt Lake City), Custom Scripts Pharmacy (Tampa, Fla.), Hal's

---

**ABBREVIATION KEY.** CPG: Compliance Policy Guide. FDA: U.S. Food and Drug Administration. FDAMA: Food and Drug Administration Modernization Act. LET: Lidocaine, adrenaline/epinephrine and tetracaine. PABA: Para-aminobenzoic acid. TAC: Tetracaine, adrenaline/epinephrine and cocaine. TADs: Temporary anchorage devices.

TABLE 1

<b>Web sites addressing the regulation of pharmaceutical compounding.</b>	
TITLE	WEB SITE
<b>U.S. FDA* Home Page</b>	<a href="http://www.fda.gov/default.htm">www.fda.gov/default.htm</a>
<b>Federal and Legal Rulings</b> <b>The 1938 Food, Drug, and Cosmetic Act</b>	<a href="http://www.fda.gov/oc/history/historyoffda/section2.html">www.fda.gov/oc/history/historyoffda/section2.html</a>
<b>FDA Modernization Act of 1997</b>	<a href="http://www.fda.gov/oc/fdama/fdamapl1n/fdamapl1n.pdf">www.fda.gov/oc/fdama/fdamapl1n/fdamapl1n.pdf</a>
<b>Legal Rulings</b> <b>Medical Center Pharmacy v. Gonzalez (2006)</b>	<a href="http://www.ncpanet.org/pdf/legal_med_center_pharm_vs_gonzales_order.pdf">www.ncpanet.org/pdf/legal_med_center_pharm_vs_gonzales_order.pdf</a>
<b>Thompson, Secretary of Health and Human Services, et al., v. Western States Medical Center, et al (2002)</b>	<a href="http://www.fda.gov/cder/pharmcomp/supremeCourt.pdf">www.fda.gov/cder/pharmcomp/supremeCourt.pdf</a>
<b>Western States Medical Center, et al., v. Donna E. Shalala, et al. (2001)</b>	<a href="http://www.fda.gov/cder/pharmcomp/westappl.pdf">www.fda.gov/cder/pharmcomp/westappl.pdf</a>
<b>Guidance for Industry</b> <b>Compliance Policy Guides Manual</b>	<a href="http://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf">www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf</a>
<b>Marketed Unapproved Drugs—Compliance Policy Guide</b>	<a href="http://www.fda.gov/cder/Guidance/6911fn1.pdf">www.fda.gov/cder/Guidance/6911fn1.pdf</a>
<b>Guide to Inspections of Topical Drug Products</b>	<a href="http://www.fda.gov/ora/Inspect_ref/igs/topic.html">www.fda.gov/ora/Inspect_ref/igs/topic.html</a>
<b>Pharmacy Compounding Advisory Committee</b>	<a href="http://www.fda.gov/cder/pharmcomp/advisorycommittee.htm">www.fda.gov/cder/pharmcomp/advisorycommittee.htm</a>
<b>FDA Public Advisory Warnings</b> <b>Warnings for Makers of Compounded Pain Products</b>	<a href="http://www.fda.gov/fdac/features/2007/207_compound.html">www.fda.gov/fdac/features/2007/207_compound.html</a>
<b>FDA Public Health Advisory</b>	<a href="http://www.fda.gov/cder/drug/advisory/topical_anesthetics.htm">www.fda.gov/cder/drug/advisory/topical_anesthetics.htm</a>
<b>Warning Letters and Notice of Violation Letters to Pharmaceuticals Companies</b>	<a href="http://www.fda.gov/cder/warn/">www.fda.gov/cder/warn/</a>
* FDA: U.S. Food and Drug Administration.	

Compounding Pharmacy (San Diego) and the New England Compounding Center (Framingham, Mass.)—to stop them from compounding and distributing standardized versions of topical anesthetic creams. The anesthetics, which contained high concentrations of local anesthetics including lidocaine, tetracaine, benzocaine and prilocaine, were being marketed for general distribution rather than being formulated for the specific medical needs of individual patients (Table 2).

According to the FDA, there have been at least two nonfatal reactions and two deaths attributed to patients' being given topical compound anesthetics to apply on their own.<sup>7</sup> The compound topical anesthetic Lasergel Plus 10/10 (compounded by Triangle Compounding Pharmacy) was associated with the death of a 22-year-old woman on Jan. 5, 2005. The compound topical anesthetic Photocaine Gel (compounded by University Pharmacy) was associated with the death of a 25-year-

old woman on Nov. 1, 2004. Both women lapsed into comas and died from lidocaine toxicity after applying the topical anesthetic to their legs and wrapping them in cellophane before laser hair removal surgery.

**Compliance policy guide.** In June 2006, the FDA issued the Marketed Unapproved Drugs—Compliance Policy Guide (CPG),<sup>8</sup> which outlines a prioritized, risk-based enforcement approach that encourages compounding pharmacies to comply with the drug-approval process and ensure the safety and efficacy of their marketed products. The issuance of the CPG was intended to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time. The highest priority will be given to drugs with potential safety risks, drugs that lack evidence of effectiveness and health fraud drugs. The FDA intends to evaluate whether justification exists to exercise enforcement on a case-by-case basis.

**DERMAL COMPOUND TOPICAL ANESTHETICS**

Practitioners should be familiar with the historical contributions of two popular compound dermal topical anesthetics: tetracaine, adrenaline/epinephrine and cocaine (TAC) and lidocaine, adrenaline/epinephrine and tetracaine (LET).

**TAC.** TAC is a compound topical gel of 0.5 percent tetracaine, 0.05 percent epinephrine and 11.8 percent cocaine.<sup>9</sup> It was the first topical anesthetic mixture found to be effective for use in simple suturing to the face and scalp.<sup>9</sup> The use of TAC gel no longer is supported in the literature owing to the general concern about toxicity, expense and federal regulatory issues involving a restricted narcotic.<sup>10,11</sup> TAC often is confused with the mucosal anesthetic compound lidocaine, tetra-

caine and phenylephrine (TAC 20 percent Alternate, Professional Arts Pharmacy, Lafayette, La.).

**LET.** LET is a compound topical gel containing 4 percent lidocaine, 0.1 percent epinephrine and 0.5 percent tetracaine.<sup>11</sup> It was created as a safer, more cost-effective alternative to TAC; it substitutes lidocaine for cocaine. It is used primarily as a dermal anesthetic for the emergency pediatric population. Early recommendations for LET use were to avoid mucosal contact; however, its active ingredients are identical to those in TAC 20 percent Alternate.

**MUCOSAL COMPOUND TOPICAL ANESTHETICS**

Two compound topical anesthetics used during placement of orthodontic TADs and soft-tissue

**TABLE 2**

**Compound topical anesthetics that received a warning from the U.S. Food and Drug Administration in 2005.**

COMMON NAME	ACTIVE INGREDIENTS*	COMPOUNDING PHARMACY
<b>Lasergel</b>	10 percent lidocaine, 10 percent tetracaine	Triangle Compounding Pharmacy (Cary, N.C.)
<b>Lasergel Plus 10/10†</b>	10 percent lidocaine, 10 percent tetracaine, 0.5 percent phenylephrine	
<b>Tetracaine Lollipops</b>	Tetracaine hydrochloride	
<b>Photocaine Gel‡</b>	6 percent lidocaine; 6 percent tetracaine	University Pharmacy (Salt Lake City)
<b>Anesthetic Skin Lotion</b>	10 percent lidocaine, 2 percent prilocaine	Hal's Compounding Pharmacy (San Diego)
<b>Anesthetic Skin Gel 3+</b>	Lidocaine, prilocaine, tetracaine	
<b>Tetracaine 6% in DMSO§ Gel</b>	6 percent tetracaine, DMSO	
<b>Triple Kwick Anesthetic Gel</b>	Benzocaine, lidocaine, tetracaine	
<b>Kwick Anesthetic Gel</b>	Benzocaine, lidocaine, tetracaine, DMSO	
<b>N*E*W Topical Anesthetic</b>	30 percent lidocaine, 2 percent prilocaine, 4 percent tetracaine	
<b>Lidocaine and Tetracaine Demi Gel</b>	Lidocaine, tetracaine	
<b>Extra Strength Triple Anesthetic Cream</b>	20 percent benzocaine, 6 percent lidocaine, 4 percent tetracaine	New England Compounding Center (Framingham, Mass.)
<b>Betacaine LA Ointment</b>	15 percent fidocaine, 5 percent prilocaine; phenylephrine	Custom Scripts Pharmacy (Tampa, Fla.)
<b>Betacaine Plus Ointment</b>	15 percent lidocaine, 5 percent prilocaine	

\* The concentration of anesthetic is provided if known.

† Lasergel Plus 10/10 (compounded by Triangle Compounding Pharmacy) has been associated with the death of a 22-year-old woman on Jan. 5, 2005.

‡ Photocaine Gel (compounded by University Pharmacy) has been associated with the death of a 25-year-old woman on Nov. 1, 2004.

§ DMSO: Dimethyl sulfoxide.



**Figure 1. A.** Application of a lidocaine, tetracaine and phenylephrine compound (TAC 20 percent Alternate) before the placement of a temporary anchorage device. **B.** Immediately after placement of the temporary anchorage device.



**Figure 2. A.** Application of a lidocaine, tetracaine and phenylephrine compound (TAC 20 percent Alternate) before laser surgery in preparation for the placement of veneers. **B.** Localized tissue irritation after prolonged application of the topical anesthetic.

laser surgery in the United States are TAC 20 percent Alternate and a lidocaine, prilocaine and tetracaine mixture (Profound)<sup>12-14</sup> (Figures 1 and 2). These “named” topical anesthetics are compounded formulations, and they should not be mistaken for regulated, manufactured drugs.

**TAC 20 percent Alternate.** TAC 20 percent Alternate is a compound topical gel containing two anesthetic agents (20 percent lidocaine and 4 percent tetracaine), one vasoactive agent (2 percent phenylephrine) and seven inactive ingredients that provide structure and give taste to the gel. Tetracaine is a long-acting ester that is included in the anesthetic to provide more profound anesthesia. The product’s name—TAC 20 percent Alternate—is a misnomer; although it is named after TAC gel, TAC 20 percent Alternate does not contain any cocaine.

**Profound and Profound PET.** Profound is a compound topical gel containing three anesthetic agents: 10 percent lidocaine, 10 percent prilocaine and 4 percent tetracaine. Profound was developed originally for use in soft-tissue laser surgery.<sup>14</sup> Its formulation is based on two FDA-approved topical anesthetics: EMLA cream (2.5 percent lidocaine,

2.5 percent prilocaine; AstraZeneca Pharmaceuticals, Wilmington, Del.), which is used to induce dermal anesthesia before venipuncture, and Oraquix (2.5 percent lidocaine, 2.5 percent prilocaine; Dentsply Pharmaceutical, York, Pa.), which is applied within the gingival sulcus before scaling and root planing.

An improved version of the original compound, Profound PET (sold as Profpet by Steven’s Pharmacy, Costa Mesa, Calif.) contains 2 percent phenylephrine and various inactive ingredients such as methylcellulose for greater viscosity.

**Application and storage.** The dosage and duration of dental compound topical anesthetics varies according to the patient and region of application. The manufacturer’s recommended dosage for Profound, Profound PET and TAC 20 percent Alternate typically is 2 milliliters applied for two to three minutes.<sup>12,14</sup> The thick, attached tissue of the palatal slope may require prolonged application for adequate anesthesia. Peak anesthesia usually is reached after five minutes and lasts approximately 25 to 30 minutes.<sup>12,14</sup>

Compound topical anesthetics may be stored at room temperature. Since phenylephrine makes



**Figure 3.** Two photographs of a lidocaine, tetracaine and phenylephrine compound ordered from two different locations of the same compounding pharmacy taken the day the anesthetics were delivered.

the topical anesthetic light sensitive with a shelf life of 90 days, those that contain phenylephrine (TAC 20 percent Alternate and Profound PET) should not be exposed to light unnecessarily.<sup>14</sup>

**Risks associated with compound topical anesthetics.** The risks associated with the use of compound topical anesthetics should be understood clearly by clinicians. Some of these risks are that

- they are packaged in vials and tubes, which makes accurate dosing difficult;
- the maximum recommended dosage is unknown, because compound topical anesthetics are meant to be custom-produced and used by only one patient;
- there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic (that is, they have a low therapeutic index);
- they may vary in their composition, the quality of the mixture and the strength of anesthesia (Figure 3);
- they often are labeled improperly and the labels fail to warn the user of risks and adverse reactions;
- they regularly include several active anesthetics, often resulting in a mixture of esters and amides.

**Contraindications and adverse drug reactions.** Clinicians who use compounded pharmaceuticals should be aware of the product's pharmacology and any contraindications.

Ester-type anesthetics (benzocaine, tetracaine) are contraindicated in patients with para-aminobenzoic acid (PABA) allergy or atypical pseudocholinesterase activity. PABA is a metabolic by-product of ester anesthetics that is known for its high allergic potential, which can lead to anaphylactic shock. Tetracaine is asso-

ciated with a higher incidence of allergic reactions than are other local anesthetics, such as lidocaine.<sup>15</sup> Ester-type anesthetics are metabolized in the bloodstream by the enzyme pseudocholinesterase. Atypical pseudocholinesterase activity (frequency, 1 per 2,800 people) is an inherited enzyme abnormality that results in a person's inability to hydrolyze ester

anesthetics and chemically related drugs such as succinylcholine.<sup>15</sup>

Amide-type anesthetics (lidocaine, prilocaine) undergo metabolic breakdown in the liver and, therefore, are contraindicated in patients with poor liver function such as cirrhosis.<sup>15</sup> Specifically, amide-type anesthetics that contain prilocaine are contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia. Prilocaine use can lead to elevated levels of methemoglobin, which decreases the ability of erythrocytes to transport oxygen, resulting in rapid cyanosis.<sup>15</sup>

In addition, direct-acting sympathomimetic agents such as phenylephrine, which can be found in TAC 20 percent Alternate and Profound PET, can cause serious adverse events related to hypertension and vasoconstriction.

The most common localized adverse reaction to compound topical anesthetics are tissue irritation (usually after prolonged application) and transitory taste perversion.

## CONCLUSIONS

In 2004, the then-editor of JADA, Dr. Marjorie K. Jeffcoat, offered simple advice to her readers with regard to the use of pharmaceutical compounds: "don't do it."<sup>24</sup> She anticipated the escalation of industry abuse, increased federal regulation and enforcement. Notwithstanding the recent FDA warnings, there still arguably is a place for doctor-prescribed, doctor-applied compound topical anesthetics for use on an individualized basis. Until these drugs become federally regulated, however, the large-scale production of some remains an end-run on manufacturing requirements, and their routine use remains a questionable therapeutic practice that may have life-threatening consequences. ■

1. United States Pharmacopeial Convention. Good compounding practices. In: *The United States Pharmacopeia: USP 28: the National Formulary: NF 23*: by authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, April 12-16, 2000. Rockville, Md.: United States Pharmacopeial Convention; 2004: 2620, 2457.
2. Department of Health and Human Services, Food and Drug Administration. Registration of producers of drugs and listing of drugs in commercial distribution—21 CFR part 207 (OMB Control Number 0910-0045)—extension. *Fed Regist* 2000;65(213):65858-9.
3. Food and Drug Administration Modernization Act of 1997, 21 USC §353A (1997).
4. Jeffcoat MK. Eye of newt, toe of frog: drug compounding: proceed with caution. *JADA* 2004;135(5):546-8.
5. U.S. Food and Drug Administration. Compliance Policy Guide: Compliance Policy Guidance for FDA Staff and Industry—Sec. 460.200, Pharmacy compounding. Available at: “[www.fda.gov/ora/compliance\\_ref/cpg/cpgdrg/cpg460-200.html](http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html)”. Accessed Aug. 7, 2007.
6. U.S. Food and Drug Administration. FDA news: FDA warns five firms to stop compounding topical anesthetic creams. Available at: “[www.fda.gov/bbs/topics/NEWS/2006/NEW01516.html](http://www.fda.gov/bbs/topics/NEWS/2006/NEW01516.html)”. Accessed Aug. 28, 2007.
7. U.S. Food and Drug Administration. FDA public health advisory: Life-threatening side effects with the use of skin products containing numbing ingredients for cosmetic procedures. Available at: “[www.fda.gov/cder/drug/advisory/topical\\_anesthetics.htm](http://www.fda.gov/cder/drug/advisory/topical_anesthetics.htm)”. Accessed Aug. 28, 2007.
8. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for FDA staff and industry: Marketed Unapproved Drugs—Compliance policy guide, Sec. 440.100 Marketed new drugs without approved NDAs or ANDAs. Available at: “[www.fda.gov/cder/guidance/6911fnl.pdf](http://www.fda.gov/cder/guidance/6911fnl.pdf)”. Accessed Aug. 29, 2007.
9. Pryor GJ, Kilpatrick WR, Opp DR. Local anesthesia in minor lacerations: topical TAC vs lidocaine infiltration. *Ann Emerg Med* 1980; 9(11):568-71.
10. Calatayud J, Gonzalez A. History of the development and evolution of local anesthesia since the coca leaf. *Anesthesiology* 2003;98(6): 1503-8.
11. Kundu S, Achar S. Principles of office anesthesia, part II: topical anesthesia. *Am Fam Physician* 2002;66(1):99-102.
12. Kravitz ND, Kusnoto B. Placement of mini-implants with topical anesthetic. *J Clin Orthod* 2006;40(10):602-4.
13. Kravitz ND, Kusnoto B, Tsay TP, Hohlt WF. The use of temporary anchorage devices for molar intrusion. *JADA* 2007;138(1):56-64.
14. Graham JW. Profound, needle-free anesthesia in orthodontics. *J Clin Orthod* 2006;40(12):723-4.
15. Malamed SF. *Handbook of local anesthesia*. St. Louis: Mosby; 1997:24-36.