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Chapter 1

Local Anesthesia

Caio Lamunier de Abreu Camargo

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Abstract

Local anesthesia is a routine procedure in dermatological practice. This chapter deals with the basic principles of pharmacology and pharmacodynamics related to the most commonly used anesthetics in dermatology as well as its side effects, the most common anesthetic solutions, anesthesia techniques, and topical anesthesia.

Keywords: anesthesia, dermatologic surgery, pharmacology, dermatology

1. Introduction

Anesthesia is a common procedure in all fields of dermatology. Knowing its pharmacological and clinical elements is essential to a good dermatological practice. Efficiency, safety, and comfort are the main concern. There are several anesthetics, and the choice of the correct one as the best application technique provides more safety, comfort, and efficiency.

It is not known exactly when the anesthesia began. Nitrous oxide is believed to have been used since 1772 by Joseph Priestley. The use of ether became famous after a public demonstration by William Thomas Green Morton in 1846, but its use is older and several other scientists have claimed the discovery of the ether as an anesthetic. The use of local anesthetics gained ground in medical science in 1884, and cocaine was widely used as a local anesthetic, although there is evidence of its use in ancient civilizations.

We can classify dermatological anesthesia in two different groups: general anesthesia and local anesthesia. General anesthesia is associated with increased risks of morbidity and mortality than local anesthesia. For this reason, local anesthesia is widely used in dermatological practice. Moreover, local anesthesia is cheaper, with less surgical time and faster recovery. Nevertheless, there are some limitations depending on the procedure's extension and patient

discomfort and collaboration. Local anesthesia can be achieved by topical products, by infiltrative nerve blocks, and by infiltrative tumescent anesthesia [1].

2. Local anesthesia

Nerve impulse transmission occurs when voltage-gated sodium channels on the neuronal membrane open, allowing massive influx of sodium into peripheral nerve cells. In resting state, the intracellular electric potential is negative relative to the extracellular space thanks to the cellular membrane and by Na^+/K^+ ATPase. The influx of sodium causes membrane depolarization and propagation of the impulse. Local anesthetics prevent nerve impulse transmission by blocking sodium channels without causing central nervous system depression or altered mental status [2, 3].

The block generally occurs in a stepwise sequence with autonomic impulses blocked first, then sensory impulses, and finally motor impulses. Unmyelinated and smaller myelinated nerve fibers are easier to block than larger myelinated fibers. Therefore, C-type fibers are the first to be blocked in a local anesthesia. Pain is first controlled followed by heat and cold sensation. Then, B-type fibers are blocked, which are the preganglionic sympathetic fibers. Finally, A-type fibers are block. Proprioception, touch and pressure, and motor fibers are the last to suffer anesthetics effects [4].

The most used anesthetic agents have three structural components: an aromatic portion, an intermediate connecting chain, and an amine portion. The aromatic portion provides hydrophobic and lipophilic properties and facilitates the diffusion of the anesthetics through nerve cell membranes. Therefore, its efficiency is improved. However, the amine portion provides lipophobic and hydrophilic properties and can become soluble for injection. The intermediate connecting chain provides the main anesthetic properties and classifies the local anesthetics into two groups: the amino amides and the amino esters [5].

Amide anesthetics—these anesthetics all have an amide linkage (i.e., bupivacaine, ropivacaine, lidocaine, prilocaine, mepivacaine). They are metabolized by microsomal enzymes in the liver and excreted by the kidneys. Decreased liver function may lead to amide anesthetics toxic effects [2, 6].

Ester anesthetics—they have an ester linkage (i.e., procaine, chloroprocaine, tetracaine, benzocaine, cocaine). The ester anesthetics use to have a shorter duration. They are hydrolyzed by plasma pseudocholinesterases and excreted by the kidneys. Decreased levels of plasma pseudocholinesterases may lead to toxic effects. The metabolite para-aminobenzoic acid (PABA) is a major metabolic product and is associated with higher incidence of allergies [2, 6].

The main properties of anesthetics are potency, toxicity, onset of action, and duration of action (**Table 1**). Lipid solubility use to be directly associated with potency as the compound penetrates the nerve cells more easily. The protein type and its capacity of maintain the sodium

channels receptor binding is association with duration of action. The dissociation constant (pKa) determines the proportion of the anesthetics base and its cation at a given pH and is associated with shorter onset of action and less toxicity. However, if the pH is raised too much, the anesthetic may precipitate out of solution [7].

Lidocaine is labeled pregnancy category B. However, it is recommended that lidocaine and all other anesthetic agents be used warily during first trimester of pregnancy. The anesthetic agents commonly cross the placenta barrier and achieve the fetus. For use in children, the maximum recommended dosage should be adjusted to child's weight. In infants, prilocaine is associated with major risk of methemoglobinemia [8] (**Tables 2** and **3**).

Anesthetic	pKa	Onset (min)	Duration (min) without epinephrine	Duration (min) with epinephrine	Max dose (mg/kg) without epinephrine	Max dose (mg/kg) with epinephrine
Chloroprocaine	9	5–6	30–60	N/A	11	14
Procaine	8.9	5	30–90	30–180	10	14
Tetracaine	8.6	7	120–240	240–480	2	2
Bupivacaine	8.1	2–10	120–240	240–480	2.5	3
Etidocaine	7.7	3–5	200	240–360	4.5	6.5
Lidocaine	7.7	<1	30–120	60–400	5	7
Mepivacaine	7.6	3–20	30–120	60–400	6	7
Prilocaine	7.7	5–6	30–120	60–400	7	10
Ropivacaine	8.2	1–15	120–360	Not yet defined	3.5	Not yet defined

Kouba et al. [9].

Table 1. Properties of local anesthetics.

		Duration (min)		Maximal recommended dose for adults	
Anesthetic	Onset (min)	Without epinephrine	With epinephrine	Without epinephrine	With epinephrine
Amides					
Articaine	2-4	30-120	60-240	5.0 mg/kg or 350 mg	7.0 mg/kg or 500 mg
Bupivacaine	2-10	120-240	240-480	2.5 mg/kg or 175 mg	3.0 mg/kg or 225 mg
Etidocaine	3-5	200	240-360	4.5 mg/kg or 300 mg	6.5 mg/kg or 400 mg
Lidocaine	<1	30-120	60-400	4.5 mg/kg or 300 mg	7.0 mg/kg or 500 mg
Mepivacaine	3-20	30-120	60-400	6.0 mg/kg or 400 mg	7.0 mg/kg or 550 mg
Prilocaine	5-6	30-120	60-400	7.0 mg/kg or 400 mg	10.0 mg/kg or 600 mg
Esters					
Chloroprocaine	5-6	30-60	N/A	11.0 mg/kg or 800 mg	14.0 mg/kg or 1000 mg
Procaine	5	15-90	30-180	10.0 mg/kg	14.0 mg/kg
Tetracaine	7	120-240	240-480	2.0 mg/kg	2.0 mg/kg

Table 2. Anesthetics used for local infiltration.

Anesthetic	Onset (min)	Duration (min)	Special considerations
Benzocaine	<5	15-45	Methemoglobinemia possible
Cocaine	1-5	30-60	
Dibucaine	<5	15-45	For mucous membranes
Dyclonine	2-10	<60	For mucous membranes but not conjunctiva
Lidocaine	<2	30-45	
Lidocaine/prilocaine eutectic mixture	<60	60-120 after removal of occlusive dressing	Only for use on intact skin, methemoglobinemia possible

Kouba et al. [9].

Table 3. Anesthetics for topical use.

3. Additions to local anesthetics

Many additives to local anesthetics have been studied. The aim of making complex anesthetic's solutions is to achieve better efficacy and safety during dermatologic surgery.

3.1. Other anesthetics

We can mix different local anesthetics in an attempt to take advantage of useful properties of each drug. For example, short-duration anesthetics like lidocaine can be mixed with a long-duration one like ropivacaine in an attempt to gain in durability. As well as, longer onset anesthetics can be mixed with shorter ones. However, this kind of association is not as logical as it seems, the nerve blockades obtained by mixing commercially available solutions of local anesthetics are unpredictable and may depend on a number of factors, which include not only the types of drugs but also the pH of the mixture. It is possible also to inject a rapid-onset anesthetic first to a longer-onset anesthetic, without mixing them [10].

3.2. Vasoconstrictors

Most local anesthetics promote vasodilatation by relaxation of vascular smooth muscle. Cocaine is the only example of local anesthetics that promotes vasoconstriction, and ropivacaine seems to be a local anesthetic that causes neither vasodilatation nor vasoconstriction. Cocaine is a norepinephrine reuptake inhibitor, thus potentiating sympathetic stimulation and causing hypertension and ventricular irritability.

Vasoconstriction at the operative site is commonly intended because it promotes less bleeding and facilitates the ease of surgery. Moreover, vasodilatation increases systemic absorption of anesthetics solution decreasing duration and efficacy of the anesthesia and increasing also systemic toxicity. Therefore, epinephrine can be useful decreasing bleeding and anesthetics systemic toxicity, and increasing their efficacy and duration [11].

Epinephrine is widely used in dermatologic surgery to promote vasoconstriction. It typically requires 5–15 min to reach full vasoconstriction effect. There are premixed solutions with epinephrine at a concentration of 1:100,000 and 1:200,000. However, effective vasoconstriction is achieved with a 1:100,000 concentration and risks of side effects are greater in 1:200,000

concentration. The maximum dose is 1 mg over approximately 8–10 h; however, this dosage should be much lower (or even absent) depending on patient age and concomitant health issues [12, 13]. Physicians using local anesthetic with epinephrine should be aware of this interaction. Epinephrine is a strong β- and α-agonist and can cause severe hypertension in patients using β-blocker medications [14]. Patients with severe cardiovascular disease may have their underlying diseases exacerbated with epinephrine use, as well as patients with narrow angle glaucoma. Patients taking monoamine oxidase inhibitors, tricyclic antidepressant, and phenothiazines are more sensitive to epinephrine. However, absolute contraindications to their use are hyperthyroidism and pheochromocytoma.

Systemic side effects of epinephrine can be self-limited or leaves to death. Therefore, it is important to avoid unintentional intravascular injection of epinephrine. Self-limited side effects include palpitations, anxiety, sweating, tremor, tachycardia, and elevated blood pressure. These signs and symptoms usually resolve within a few minutes, but the patient must be under continuous monitorization to identify a serious side effect. Serious side effects of epinephrine include cardiovascular and cerebral suffering. Arrhythmias, tachycardias, and ventricular fibrillation are between the most common severe side effects.

Epinephrine is labeled pregnancy category C. The effect of pregnancy on arterial sensitivity to vasoconstrictors is controversial. Pregnancy was demonstrated to be associated with a significant reduction in both uterine artery response and sensitivity to norepinephrine, epinephrine, and phenylephrine. However, there was no consistent pregnancy-associated effect on carotid artery response and sensitivity [15]. This reduction in artery response can be related to a fetal suffering, particularly in the first semester, and a premature labor in the third semester. Thereby, it is prudent to postpone nonurgent procedures requiring the use of epinephrine until after pregnancy.

Epinephrine found commercially available with lidocaine in premixed solutions contains acidic preservatives, such as sodium metabisulfite and citric acid [16]. As lower pH solutions use to cause more pain on injection, fresh lidocaine and epinephrine solutions are preferred than commercially lidocaine and epinephrine solutions [17].

The use of epinephrine on digits may prolong the duration of anesthesia and reduce the risk of bleeding during surgery, but it has been associated once with digital necrosis caused by vasoconstriction. Recent big studies recurrently demonstrate that evidence is insufficient to recommend use or avoidance of adrenaline in digital nerve blocks. However, there are case reports describing digital necrosis after injection of lidocaine with epinephrine. These digital necrosis cases can be as associated with vessel compression, constricting circumferential dressings, tourniquets, infection, hematoma, or patient's vascular disease. In absence of these conditions, the use of epinephrine on digits seems to be safe. However, if a tourniquet is used during the surgery, there is no benefit of using also epinephrine to control bleeding [18–20].

3.3. Sodium bicarbonate

Lower pH solutions use to cause more pain on injection [17]. That is why the pain of infiltrating lidocaine with epinephrine into skin is reduced by the addition of sodium bicarbonate.

Adding sodium bicarbonate to anesthetic solution of lidocaine plus epinephrine in a proportion of 1–10 can raise the solution's pH from approximately 5.0 to approximately 7.5. As epinephrine concentration declined approximately 25% per week in anesthetic solution containing sodium bicarbonate, it is recommended to use fresh solutions [21, 22].

In addition, alkalinization of local anesthetics solutions leads to a faster onset of action and a better anesthetic efficacy. However, it declines the duration of both anesthesia and vasoconstriction.

3.4. Hyaluronidase

Hyaluronidase is an enzyme that depolymerizes hyaluronic acid. Despite it is famous in correcting acid hyaluronic fillers defect, it can be used in dermatologic surgery as an addition to local anesthetics by facilitating diffusion of solutions through tissue planes further away from the injection point. Although the duration of anesthesia is slightly decreased, the addition of hyaluronidase to local anesthesia offers the benefits of minimizing loss of surface contour and enhanced ease in undermining and dissection through subcutaneous tissue planes [23, 24].

The decrease of anesthesia's duration and the major toxicity are explained due to increased absorption of the solution. That is why the tumescent technique must be avoided in hyaluronidase solution. The dosage usually recommended is one ampule to 30 ml anesthetic solution.

4. Side effects

Local anesthetics side injection frequently causes pain and local edema. Transient bruise and motor nerve paralysis can also occur. These are common local side effects. More rarely is nerve injuries. Intraneural injection can cause nerve damage and prolonged sensory nerve paresthesia may develop.

Despite local anesthetic systemic toxicity (LAST) is relatively rare, it must be considered whenever local anesthetic is administered. Difficulties in the clearance of these drugs can also be an important cause of LAST.

Central nervous system toxicity is due to intracellular voltage-gated fast sodium channels blockage in neuronal tissue. It all begins with blockade of cerebral cortical inhibitory pathways, leading to excitation, sensory and visual disturbance, muscle twitching, and convulsions. Perioral paresthesia is a classic early manifestation of LAST. CNS depression comes later with dizziness, confusion, unconsciousness, coma, and respiratory arrest [25].

Cardiovascular toxicity can be expressed by different kinds of arrhythmias. Local anesthetics block sodium channels in cardiovascular conducting cells and reduce the rate of depolarization and propagation of action potentials. Thereby, PR, QRS, and ST intervals become larger increasing the risk of bradyarrhythmia and re-entrant tachyarrhythmias. Myocardial depression and changes in systemic vascular resistance is also described. Among the commonly used local anesthetics, bupivacaine is the most cardiotoxic one [26].

Usually, central nervous systemic toxicity signs precede cardiovascular toxicity signs whereas it is not a rule. The majority of LAST events occurs within several minutes of local anesthetics injection, but onset of symptoms can be delayed up to 60 min. Intra-arterial injection of anesthetics deflagrates almost immediately the LAST symptoms, as in intravenous injection or in systemic abortion, and there is a delay in the onset of signs [27].

Risk factors for LAST include drug pharmacological properties, administration dynamics, and patient factors. Local anesthetics should be reduced by 15% in babies less than 4 months old due to immaturity of hepatic enzymes [28]. Elderly people can have clearance of anesthetics reduced. Renal dysfunction is not related to more LAST and routine dose reduction is usually unnecessary. Hepatic dysfunction is offset by an increased volume of distribution of anesthetic agents and injections doses should be limited accordingly to the severity of hepatic dysfunction. Severe cardiac dysfunction can cause reduced hepatic and renal perfusion taking to clearance deficiency. Pregnant patients also can have increased cardiac output in second and third semester pregnancy [29].

There are maximum doses permissible for each anesthetic agent, and it is usually bigger when vasoconstrictors are associated. However, LAST may occur despite adherence to these limits. Therefore, practitioners should always use the lowest dose necessary to achieve the desired result due to the significant risk of systemic toxicity [30].

Besides respect the maximum anesthetics dosage, it is important to avoid intravascular injection. Ultrasound-guided peripheral nerve blockade reduces risk of LAST [31].

The management of LAST is mainly clinical support. Intravenous access, oxygen, and standard monitoring should be a routine for all patients with suspect of LAST. However, there are other clinical evidences that must be distinct of LAST, as vasovagal or allergic reactions [32].

Vasovagal reactions are by far the most common situation that must be distinct of LAST. Patient anxiety can result in an increase in parasympathetic tone. Dizziness, nausea, distal paresthesia, and hypotension are the main symptoms [33].

Although allergic reactions to anesthetics are commonly reported, true allergic reactions are actually rare. Local anesthetics are too small to be antigenic by themselves but are sufficiently alien to bind as haptens to tissues with antigenic properties. Up to 14 days are required to develop sensitization (antibody production). Once sensitization occurs, exposure to fractional quantities of the offending agent invokes an antigen-antibody reaction. Responses are classified into four categories depending upon the response. Type I reactions are IgE-mediated and are characterized by a massive release of histamine, serotonin, leukotrienes, and other humoral substances from mast cells resulting in a sudden onset of bronchospasm, cardiovascular depression and airway compromise, otherwise known as anaphylaxis. This is a true medical emergency and requires immediate and aggressive treatment. Type IV reactions represent the other end of the spectrum. Characteristically, they have a slower onset, associated with a non-IgE mediated release of bioamines, including histamine. The severity of the reaction depends on the quantity of the mediator released and can vary from mild contact dermatitis to anaphylactoid shock [34, 35].

Allergies have been reported for each class of local anesthetics, but cross-over sensitivity does not occur. Ester local anesthetics are metabolized to a PABA-like compound, and anaphylaxis

has been reported. Amide local anesthetics sometimes contain the preservative methylparaben, which has also been reported to cause severe allergic reactions. It is important to know which class of local anesthetic caused the reaction and avoid that class in the future [2].

Taking a thorough history in these cases and reviewing all relevant medical and dental records are the best way of doing it. Allergists usually carry out skin testing whereas they are equivocal in a large percentage of cases [34].

5. Topical anesthetics

Topical anesthetics act on the peripheral nerve endings in the dermis or mucosa, reduce the sensation of pain at the site of application, and avoid local pain caused by needling. They are useful aids during dermatologic treatment, especially in children, by mitigating discomfort and pain. Topical anesthetics also avoid tissue edema and surgical site distortions [36].

Their delivery and effectiveness can be enhanced by using free bases, by increasing the drug concentration, lowering the melting point, by using physical and chemical permeation enhancers and lipid delivery vesicles. Topical anesthetics are also able to penetrate mucosal surfaces, such as the mouth, genitals, and conjunctiva more easily than through a keratinized surface because of the absence of a stratum corneum [37].

Topical anesthetics seem to be safe, whereas systemic absorption occurs and systemic toxic events must be prevented. Extra caution is needed in damaged skin barrier, in infants, in mucosa, and in the extension of the applied corporal area [38].

The discovery of various amide and ester local anesthetics, their topical preparations and delivery systems in due course of time opened the gate of immense possible uses of topical anesthetics. The main topical anesthetics for mucous membrane and intact skin are benzocaine, dibucaine, lidocaine, prilocaine, proparacaine, and tetracaine. They exist in isolated form or in mixed different formulas.

Cryoanesthesia is the reduction of pain by applying cold agents to the skin. Various topical freezing agents are available: applying ice to the skin, the use of cooled gel or a cold glass, vapocoolant equipments, and cryogen sprays. The efficacy of cryoanesthesia is variable, and it has risk of causing scars and hyper or hypopigmentation [39].

6. Anesthetic injection techniques

Local anesthetic injection is often cited in literature as the most painful part of minor procedures. It is also very possible for all doctors to get better at giving local anesthesia with less pain for patients [40].

The pain of needle insertion can be reduced by verbal distraction, massage at neighborhood of the local of injection, pinching, quick and right need injection, the use of previously topic

anesthetics, and accessory vibratory and cooler equipments. Small needles are related to less pain also. Additional sticks should be through an already numb area, and the injection should start on the side that the sensory innervations are coming from.

Sometimes, the injection of the anesthetic solution is more painful than the needle insertion itself due to tissue distension and solutions' pH. To minimize tissue distension, the slowly injection of the anesthetic fluid is recommended. This is better obtained by the use of smaller needles and syringes. Subcutaneous injections promote less pain because of better tissue distension than intradermal injection. Acid solutions are usually associated with major pain. That is one reason why doctors associate sodium bicarbonate with anesthetic solutions. Intracutaneous instillation of lidocaine at body temperature is no less painful than injection at lower temperature [41].

Nerve block anesthesia also can minimize multiple anesthetics injection, besides decreasing the amount of solution need and its side effects. It is good to anesthetize large areas with little surface distortion. In general, nerve blocks cause less discomfort to the patient, especially during a mucosal approach. The correct technique involves injection of the anesthetic solution around the nerve, never into the nerve, to avoid nerve injuries. It is important to remember the presence of accompanying vein and artery to the nerve. Caution is needed to prevent intravascular injection. Intraforaminal injection is not recommended due to nerve compression. It is recommended to wait for about 5–10 min for full effectiveness of nerve blocks [4].

Field block anesthesia is a technique used mainly in cyst and skin cancer surgery. Field block anesthesia involves injecting anesthetic solution around the proposed surgical site, thereby blocking surrounding innervations. It is useful to avoid tumor transection. There are case reports of neoplasm surgical skin implantation. That is why field block anesthesia is recommended. Puncturing the cyst during surgery should also be avoided to decrease cyst recurrent [42].

Tumescent anesthesia is technique, which consists in infiltrating a large volume of dilute anesthetic and epinephrine solution to produce swelling and firmness of the target areas. It was first described by Kein and Lillis for liposuction surgery. The tumescent technique for local anesthesia has made it possible to do liposuction, dermabrasion, facelifts, carbon dioxide laser full-face resurfacing, hair transplants, and large cutaneous excisions and repairs totally by local anesthesia without intravenous sedation or narcotic analgesia. These benefits are optimizing biochemical compartments, maximizing drug concentration locally, delaying systemic drug absorption, decreasing systemic toxicity, prolonging local anesthetic effects, and benefiting from augmented local hydrostatic pressure to reduce bleeding and facilitate tissue dissection [43, 44]. Lidocaine is the most used anesthetic agent, whereas prilocaine also seems to be safe and effective [45]. There is no data examining other anesthetics for use in tumescent local anesthesia.

Author details

Caio Lamunier de Abreu Camargo

Address all correspondence to: caiolamunier@yahoo.com.br

Universidade de São Paulo (USP), São Paulo, Brazil

References

[1] Koay J, Orengo I. Application of local anesthetics in dermatologic surgery. Dermatologic Surgery. 2002 Feb;**28**(2):143-148

[2] Garmon EH, Dulebohn SC. Topical, Local, and Regional Anesthesia and Anesthetics. StatPearls Publishing; 2017 June

[3] Ragsdale DS, McPhee JC, Scheuer T, Catterall WA. Molecular determinants of state-dependent block of Na+ channels by local anesthetics. Science. 1994 Sep 16;**265**(5179):1724-1728

[4] Grekin RC, Auletta MJ. Local anesthesia in dermatologic surgery. Journal of the American Academy of Dermatology. 1988 Oct;**19**(4):599-614

[5] Covino BG. Local anesthesia. 1. The New England Journal of Medicine. 1972 May 4;**286**(18):975-983

[6] Covino BG. Local anesthesia. 2. The New England Journal of Medicine. 1972 May 11;**286**(19):1035-1042

[7] Covino BG. Pharmacology of local anesthetic agents. Rational Drug Therapy. 1987 Aug;**21**(8):1-9

[8] Richards KA, Stasko T. Dermatologic surgery and the pregnant patient. Dermatologic Surgery. 2002 Mar;**28**(3):248-256

[9] Kouba DJ, LoPiccolo MC, Alam M, Bordeaux JS, Cohen B, Hanke CW, Jellinek N, Maibach HI, Tanner JW, Vashi N, Gross KG, Adamson T, Begolka WS, Moyano JV. Guidelines for the use of local anesthesia in office-based dermatologic surgery. Journal of the American Academy of Dermatology. 2016 Jun;**74**(6):1201-1219

[10] Galindo A, Witcher T. Mixtures of local anesthetics: Bupivacaine-chloroprocaine. Anesthesia and Analgesia. 1980 Sep;**59**(9):683-685

[11] Covino BG. Pharmacology of local anaesthetic agents. British Journal of Anaesthesia. 1986 Jul;**58**(7):701-716

[12] Siegel RJ, Vistnes LM, Iverson RE. Effective hemostasis with less epinephrine. An experimental and clinical study. Plastic and Reconstructive Surgery. 1973 Feb;**51**(2):129-133

[13] Fante RG, Elner VM. The use of epinephrine in infiltrative local anesthesia for eyelid reconstruction. Plastic and Reconstructive Surgery. 1998 Sep;**102**(3):917

[14] Foster CA, Aston SJ. Propranolol-epinephrine interaction: A potential disaster. Plastic and Reconstructive Surgery. 1983 Jul;**72**(1):74-78

[15] Weiner CP, Martinez E, Chestnut DH, Ghodsi A. Effect of pregnancy on uterine and carotid artery response to norepinephrine, epinephrine, and phenylephrine in vessels with documented functional endothelium. American Journal of Obstetrics and Gynecology. 1989 Dec;**161**(6 Pt 1):1605-1610

[16] Moore DC. The pH of local anesthetic solutions. Anesthesia and Analgesia. 1981 Nov;**60**(11):833-834

[17] Howe NR, Williams JM. Pain of injection and duration of anesthesia for intradermal infiltration of lidocaine, bupivacaine, and etidocaine. The Journal of Dermatologic Surgery and Oncology. 1994 Jul;**20**(7):459-464

[18] Prabhakar H, Rath S, Kalaivani M, Bhanderi N. Adrenaline with lidocaine for digital nerve blocks. Cochrane Database of Systematic Reviews. 2015 Mar 19;**3**

[19] Denkler KA. Epinephrine in the digits. Plastic and Reconstructive Surgery. 2011 Aug;**128**(2):598-599

[20] Denkler K. Myth of not using lidocaine with epinephrine in the digits. American Family Physician. 2010 May 15;**81**(10):1188

[21] McKay W, Morris R, Mushlin P. Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. Anesthesia and Analgesia. 1987 Jun;**66**(6):572-574

[22] Stewart JH, Cole GW, Klein JA. Neutralized lidocaine with epinephrine for local anesthesia. The Journal of Dermatologic Surgery and Oncology. 1989 Oct;**15**(10):1081-1083

[23] Lewis-Smith PA. Adjunctive use of hyaluronidase in local anaesthesia. British Journal of Plastic Surgery. 1986 Oct;**39**(4):554-558

[24] Clark LE, Mellette JR Jr. The use of hyaluronidase as an adjunct to surgical procedures. The Journal of Dermatologic Surgery and Oncology. 1994 Dec;**20**(12):842-844

[25] Di Gregorio G, Neal JM, Rosenquist RW, Weinberg GL. Clinical presentation of local anesthetic systemic toxicity: A review of published cases, 1979 to 2009. Regional Anesthesia and Pain Medicine. 2010 Mar-Apr;**35**(2):181-187

[26] Groban L. Central nervous system and cardiac effects from long-acting amide local anesthetic toxicity in the intact animal model. Regional Anesthesia and Pain Medicine. 2003 Jan-Feb;**28**(1):3-11

[27] Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: Incidence and preventive measures. Regional Anesthesia and Pain Medicine. 2002 Nov-Dec;**27**(6):556-561

[28] Meunier JF, Goujard E, Dubousset AM, Samii K, Mazoit JX. Pharmacokinetics of bupivacaine after continuous epidural infusion in infants with and without biliary atresia. Anesthesiology. 2001 Jul;**95**(1):87-95

[29] Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: A multifactorial concept. Regional Anesthesia and Pain Medicine. 2004 Nov-Dec;**29**(6):564-575 discussion 524

[30] Neal JM, Bernards CM, Butterworth JF 4th, Di Gregorio G, Drasner K, Hejtmanek MR, Mulroy MF, Rosenquist RW, Weinberg GL. ASRA practice advisory on local anesthetic systemic toxicity. Regional Anesthesia and Pain Medicine. 2010 Mar-Apr;**35**(2):152-161

[31] Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Regional Anesthesia and Pain Medicine. 2013 Jul-Aug;**38**(4):289-299

[32] El-Boghdadly K, Chin KJ. Local anesthetic systemic toxicity: Continuing professional development. Canadian Journal of Anaesthesia. 2016 Mar;**63**(3):330-349

[33] Baluga JC. Allergy to local anesthetics in dentistry. Myth or reality? Revista Alergia México. 2003 Sep-Oct;**50**(5):176-181

[34] Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: Separating fact from perception: A UK perspective. British Journal of Anaesthesia. 2012 Jun;**108**(6):903-911

[35] Finucane BT. Allergies to local anesthetics—The real truth. Canadian Journal of Anaesthesia. 2003 Nov;**50**(9):869-874

[36] Lee HS. Recent advances in topical anesthesia. Journal of Dental Anesthesia and Pain Medicine. 2016 Dec;**16**(4):237-244

[37] Kumar M, Chawla R, Goyal M. Topical anesthesia. Journal of Anaesthesiology Clinical Pharmacology. 2015 Oct-Dec;**31**(4):450-456

[38] Sobanko JF, Miller CJ, Alster TS. Topical anesthetics for dermatologic procedures: A review. Dermatologic Surgery. 2012 May;**38**(5):709-721

[39] Plotkin S. Clinical comparison of preinjection anesthetics. Journal of the American Podiatric Medical Association. 1998 Feb;**88**(2):73-79

[40] Strazar AR, Leynes PG, Lalonde DH. Minimizing the pain of local anesthesia injection. Plastic and Reconstructive Surgery. 2013 Sep;**132**(3):675-684

[41] Arndt KA, Burton C, Noe JM. Minimizing the pain of local anesthesia. Plastic and Reconstructive Surgery. 1983 Nov;**72**(5):676-679

[42] Auletta MJ. Local anesthesia for dermatologic surgery. Seminars in Dermatology. 1994 Mar;**13**(1):35-42

[43] Klein JA. Tumescent technique chronicles. Local anesthesia, liposuction, and beyond. Dermatologic Surgery. 1995 May;**21**(5):449-457

[44] Behroozan DS, Goldberg LH. Dermal tumescent local anesthesia in cutaneous surgery. Journal of the American Academy of Dermatology. 2005 Nov;**53**(5):828-830

[45] Augustin M, Maier K, Sommer B, Sattler G, Herberger K. Double-blind, randomized, intraindividual comparison study of the efficacy of prilocaine and lidocaine in tumescent local anesthesia. Dermatology. 2010;**221**(3):248-252