Guidelines for the use of local anesthesia in office-based dermatologic surgery

Work Group: Chair, David J. Kouba, MD, PhD,[a] Matteo C. LoPiccolo, MD,[a,b,c] Murad Alam, MD,[d] Jeremy S. Bordeaux, MD, MPH,[e] Bernard Cohen, MD,[f] C. William Hanke, MD,[g] Nathaniel Jellinek, MD,[h] Howard I. Maibach, MD,[i] Jonathan W. Tanner, MD, PhD,[j] Neelam Vashi, MD,[k] Kenneth G. Gross, MD,[l] Trudy Adamson, MSN, RN, DNC,[m] Wendy Smith Begolka, MBS,[n] and Jose V. Moyano, PhD[n]

Toledo and Cleveland, Ohio; Detroit and Shelby, Michigan; Chicago and Schaumburg, Illinois; Baltimore, Maryland; Carmel, Indiana; East Greenwich, Rhode Island; San Francisco and San Diego, California; Philadelphia, Pennsylvania; Boston, Massachusetts; and Rochester, Minnesota

There are an increasing number and variety of dermatologic surgical procedures performed safely in the office setting. This evidence-based guideline addresses important clinical questions that arise regarding the use and safety of local anesthesia for dermatologic office-based procedures. In addition to recommendations for dermatologists, this guideline also takes into account patient preferences while optimizing their safety and quality of care. The clinical recommendations presented here are based on the best evidence available as well as expert opinion. (J Am Acad Dermatol 2016;74:1201-19.)

Key words: anesthesia; clinical guideline; dermatology; education; epinephrine; infiltration; local anesthesia; local nerve block; office-based surgery; pain; safety; topical; tumescent.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy and/or technique must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biological behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline addresses the clinical use and safety of local anesthetics (ie, topical, infiltrative, nerve blocks, and infiltrative tumescent) commonly used in office-based dermatologic surgery for adult and pediatric patients. While anxiolytics, sedatives, and other systemic medications may be used for office-based procedures, these methods are not discussed in this guideline because they are forms of systemic and not local anesthesia. Anesthetic toxicity is rare in the dermatologic office setting, and therefore management of local anesthetic

From the Toledo Clinic Facial Plastics and Dermatology[a]; Department of Dermatology,[b] Henry Ford Health System, Detroit; Dermatology Specialists of Shelby[c]; Department of Dermatology,[d] Northwestern Memorial Hospital, Chicago; Department of Dermatology,[e] University Hospitals Case Medical Center, Cleveland; Department of Dermatology-Pediatrics,[f] Johns Hopkins Children's Center, Baltimore; Laser and Skin Surgery Center of Indiana PC,[g] Carmel; Department of Dermatology,[h] Brown University, East Greenwich; Department of Dermatology,[i] UCSF School of Medicine, San Francisco; Department of Anesthesiology and Critical Care,[j] University of Pennsylvania, Philadelphia; Department of Dermatology and Center for Ethnic Skin,[k] Boston University School of Medicine; Skin Surgery Medical Group, Inc,[l] San Diego; Department of Nursing,[m] Mayo Clinic College of Medicine, Rochester; and the Department of Science, Quality and Practice,[n] American Academy of Dermatology, Schaumburg.

Funding sources: None.

This guideline was developed in accordance with the Academy's Administrative Regulations for Evidence-Based Guidelines, and followed a strong disclosure and conflict of interest management plan consistent with Institute of Medicine and Council of Medical Specialty Society standards. The authors' conflict of interest disclosure statements appear at the end of this article.

Accepted for publication January 15, 2016.

Reprint requests: Jose V. Moyano, PhD, 930 E Woodfield Rd, Schaumburg, IL 60173. E-mail: guidelines@aad.org.

Published online March 4, 2016.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2016.01.022

toxicity is not addressed in this guideline. Other aspects, such as physician and staff certification, credentialing and privileging, facility accreditation, office equipment and set-up requirements, and legal/regulatory compliance, or any other administrative requirements and regulations, fall beyond the scope of this guideline.

METHODS

A work group composed of 8 dermatology experts practicing in office settings and in academic institutions, 1 anesthesiologist, and 1 patient advocate was convened to determine the scope of the guideline, and to identify important clinical questions (Table I) in the use and safety of local anesthesia in office settings. Work group members completed a disclosure of interests, which was periodically updated and reviewed throughout guideline development. If a potential conflict was noted, the work group member recused him or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

Evidence was obtained for the clinical questions determined by the work group using a systematic search of PubMed and Google Scholar databases between the years of 1960 and 2014. Searches were prospectively limited to publications in the English language. MeSH terms and strings used in the literature search included: dermatology, skin, office-based surgery, local anesthesia, infiltration, topical anesthesia, lidocaine, tetracaine, prilocaine, marcaine, bupivacaine, etidocaine, mepivacaine, procaine, ester, amide, structure, comparison, efficacy, safety, risk, nerve blocks, tissue, face, head, neck, nose, ear, eye, lid, hands, feet, digits, penis, genitals. pregnancy, pediatrics, pain, tissue absorption, dose, time, slow, fast, volume, pharmacokinetics, serum levels, technique, method, laser, ethyl chloride, symptoms, systemic, toxicity, local anesthetic systemic toxicity (LAST), treatment, prevention, epinephrine, adrenaline, vasoconstriction, hyaluronidase, mixtures, solution, needle, cannula, sodium bicarbonate, pH, infusion rate, and tumescent anesthesia.

A total of 599 abstracts were initially assessed for possible inclusion. After removal of duplicate data and nonrelevant studies, 165 abstracts were retained and used for a secondary, manual search identifying 36 additional relevant studies. Once the full data set of 201 studies was collated, each study was reviewed and ranked based on relevance and the level of evidence for the outlined clinical questions. Evidence tables were generated for these studies and used by the work group in developing recommendations.

The available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) that was developed by editors of the United States family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).[1] Evidence was graded using a 3-point scale based on the quality of methodology (eg, randomized control trial, case control, prospective or retrospective cohorts, case series, etc) and the overall focus of the study (ie, diagnosis, treatment, prevention, screening, or prognosis) as follows:

I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients, including morbidity, mortality, symptom improvement, cost reduction, and quality of life).
II. Limited-quality patient-oriented evidence (ie, lower quality clinical trials, cohort studies, and case control studies).
III. Other evidence including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed based on the best available evidence tabled in the guideline. The strength of recommendation was ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In situations where documented evidence-based data were not available, or showing inconsistent or limited conclusions, expert opinion and medical consensus were used to generate clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (AAD)/AAD Association Administrative Regulations for Evidence-based Clinical Practice Guidelines (version approved August 2012), which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.[2] This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

DEFINITION

The definition of office-based surgery varies by state and regulatory agency. For the purpose of this

Table I. Clinical questions used to structure the evidence review for the use of local anesthesia in the office-based setting

Topical anesthesia
A. Is topical anesthesia safer/more effective than other types of anesthesia to reduce pain?
B. Are the same topical anesthetics used in adults also recommended/safe in pregnancy and lactation?
C. Are the same topical anesthetics used in adults also recommended/safe in children?
Local infiltration anesthesia
A. Is local infiltration anesthesia safer/more effective than other types of anesthesia to reduce pain?
B. Does the method to calculate the maximum anesthetic doses change when infiltrated anesthetics are delivered over an extended time period compared to a short time period?
C. Do the local anesthetic serum levels change based on the method of delivery?
D. Is there a measure of care better/safer than others in decreasing the symptoms of systemic toxicity?
E. Does the addition of epinephrine to infiltrated anesthetics increase safety risks in cardiac and pregnant patients, or for use in the digits, nose, and penis, compared to infiltrated anesthetics alone?
F. Is a lower concentration of epinephrine as effective as high concentrations added to infiltrated anesthetics to produce vasoconstriction?
G. Do the maximum recommended doses and delivery methods both in adults and children differ by the addition of epinephrine?
H. Does the addition of hyaluronidase increase the diffusion rate and effectiveness/safety of infiltrative anesthetics?
I. Does mixing multiple anesthetics pose a benefit to the patient compared to a single anesthetic for the same procedure?
J. Does the addition of sodium bicarbonate to anesthetics decrease patients' pain when administered by subcutaneous infiltration?
K. Does the use of a particular injection represent a clinical benefit for the patient?
L. Does the use of other commonly used techniques minimize pain?
Nerve block/regional anesthesia
A. Does nerve block/regional anesthesia represent a clinical benefit over local infiltrative anesthesia for the head and neck, hands, feet, and genitals?
B. Does the injection of local anesthesia in the optimal entry points for the head and neck, hands, feet, and genitals pose an increased risk of nerve damage from needle trauma and of toxicity?
Tumescent anesthesia
A. Is the use of lidocaine in tumescent anesthesia safer than other anesthetics for the same procedure?
B. Does the volume and dose of lidocaine and epinephrine correlate with patient safety in tumescent anesthesia?
C. Does a slow infusion rate result in less pain or a better anesthetic effect than fast infusion rates?
D. Is there a measure of care better/safer than others to decrease symptoms of local anesthetic systemic toxicity for patients anesthetized using the tumescent technique?

clinical guideline, office-based dermatologic surgery is defined as surgery performed by a licensed physician to diagnose and treat certain skin conditions using topical, local, infiltrative, or tumescent local anesthesia in an office or facility outside of ambulatory surgical centers and hospital settings.

INTRODUCTION

There are a large variety of skin conditions that require surgical intervention for proper diagnosis and management. Most, if not all, of these procedures may be safely performed in the dermatology office with the patient under local anesthesia.[3,4] A myriad of medications and techniques are available for use, and selection of local anesthesia is largely based upon the experience and comfort level of the clinician, but is also impacted by patient factors and concerns. Certain patient populations, such as those with red hair or African Americans, seem to be more sensitive to pain and to require higher doses to achieve similar anesthesia, with the concomitant increased risk of adverse effects.[5-8] A list of local anesthetics for use in the office setting is provided in Tables II and III. This guideline is created to facilitate the selection of the most effective means of achieving local anesthesia for a variety of cutaneous procedures while also minimizing the risk of adverse events. In cases where clinical evidence to make a recommendation is insufficient or lacking, the experience of the expert panel is presented and gaps in data are identified in order to guide future research.

TOPICAL ANESTHESIA

The recommendations for topical anesthesia and the strength of evidence are listed in Tables IV and V, respectively.

Safety and efficacy

Many topical anesthetic agents are effective and safe for use in dermatologic procedures with a low

Table II. Anesthetics used for local infiltration[3,9-11]

Anesthetic	Onset (min)	Duration (min)		Maximal recommended dose for adults	
		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 III. Anesthetics for topical use[10,11]

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

risk of adverse events.[13,34,35] However, caution must be taken when occlusion is used or large surface areas are treated because there are no data supporting standard practice. This is particularly true with compounded mixtures and nonstandard doses, which although rarely used by dermatologists may increase the risk of adverse events and even death.[36-38] Data comparing these agents in dermatology are limited to 1 prospective study that found 4 topical preparations to be equivalent in reducing pain sensation for use in nonablative laser therapy.[39] More extensive research has been conducted in emergency and obstetric settings, which has also shown multiple topical anesthetics to be equally effective for wound repair.[12,15,16]

The advent of many effective noncocaine formulations in the 1990s has raised the question of whether the use of cocaine in topical anesthesia is necessary. A systematic review of 22 trials encompassing >3000 patients was conducted to identify noncocaine anesthetics that were potentially less costly yet equally effective as those that contain cocaine.[12] The review found no significant difference in efficacy among topical tetracaine-epinephrine-cocaine and 6 different cocaine-free formulations, but the addition of cocaine was associated with a higher cost and potential for adverse effects. Although no firm recommendation supporting the use of any single noncocaine formulation over another can be made, it is the opinion of this work group that because of the increased cost and potential for adverse events, noncocaine anesthetics are preferred over those containing cocaine for use in office-based dermatologic surgery.

In certain situations, topical agents may offer similar analgesia to that of infiltrated anesthetics. Studies comparing topical to infiltrative anesthesia, including a systematic review, found the 2 methods to have equivalent efficacy in episiotomy repair, split-thickness skin graft harvest, manipulation of the fractured nose, arterial cannulation, and minor laceration repair.[12,15-19] For the latter indication, topical agents were particularly useful for face and scalp wounds, where absorption may be highest.[19] Most of these studies noted more patient discomfort associated with the injection of infiltration anesthesia than the application of topical anesthetic. In addition, single studies found topical anesthesia alone to be sufficient for cauterization or excision of genital warts in 97% of men (55 of 57 patients)[20] and of skin lesions ≤40 mm in diameter on the trunk or extremities in 87% of adults (92 of 106 patients)[21]—although the degree of repair was not stated. Extrapolation from these data suggests that topical anesthesia alone may

Table IV. Recommendations for the use of topical anesthesia in dermatologic surgery

Noncocaine formulations are preferred over cocaine formulations and recommended for use in office-based procedures
Topical agents are recommended as a first-line method of anesthesia for nonablative laser treatments
Topical anesthesia can be used for performing office-based procedures, such as skin biopsy, small excisions, and filler and botulinum toxin injections
The use of topical anesthetic agents is recommended to lessen the pain of injection and reduce the dose of infiltration anesthesia needed for larger procedures
Topical lidocaine is safe for use on pregnant or nursing women, but there is insufficient evidence to recommend use of other topical anesthetics
Elective procedures and those not of urgent medical necessity requiring topical lidocaine in pregnant women should be postponed until after delivery
Procedures of urgent medical necessity should be delayed until at least the second trimester when possible
Topical agents are recommended as a first-line method of anesthesia for the repair of dermal lacerations in children and for other minor dermatologic procedures, including curettage. For skin biopsy, excision, or other cases where topical agents alone are insufficient, adjunctive use of topical anesthesia to lessen the discomfort of infiltrative anesthetic should be considered
For more extensive surgery, the combination of topical and infiltration anesthesia should be considered as an alternate to sedation or general anesthesia in pediatric patients

Table V. Strength of recommendations for use of topical anesthesia in dermatologic surgery

Recommendation	Strength of recommendation	Level of evidence	References
Use of noncocaine topical anesthetics	A	II	12
Topical anesthesia as the first-line method for nonablative laser treatments	C	III	13,14
Topical anesthesia for use in minor skin procedures in adults	C	III	13-21
Topical anesthesia to reduce the pain of local anesthetic injection	C	III	Expert opinion
Use of limited amounts of topical lidocaine in pregnant and nursing women	C	III	22-25
Postpone use of topical anesthesia until after delivery or second trimester when possible	C	III	Expert opinion
Against use of nonlidocaine topical anesthetics in pregnant or nursing women	C	III	Expert opinion
Use of topical anesthesia as the first-line method for repair of dermal lacerations in children	A	I, II	19,26-31
Use of topical anesthesia as the first-line method for other minor procedures in children	C	III	Expert opinion
Adjunctive use of topical anesthesia to minimize discomfort of infiltrative anesthesia in children	C	III	Expert opinion
Topical and infiltrative anesthesia used as an alternate to sedation and general anesthesia in children	C	III	19,26-33

be acceptable for minor skin surgeries and can be considered as an alternate to infiltration anesthesia.

The area in which topical anesthesia is perhaps most consistently used in dermatology is for cutaneous laser procedures. In the experience of the work group, topical agents achieve anesthesia that is adequate for a variety of nonablative laser treatments. Expert experience and limited data from the literature suggest that topical anesthesia alone may even be sufficient to perform ablative laser resurfacing for some patients, but more often is used in combination with infiltrative anesthesia or cutaneous nerve blocks in these procedures.[13,14] In the opinion of the expert panel, topical anesthesia is also helpful to enhance patient comfort during injections of subcutaneous filler and botulinum toxin. In cases where infiltration anesthesia is necessary, the experience of the work group supports the adjunctive use of topical agents to reduce the effective dose and the pain of injection of local anesthetic.

Further study into the use of these agents would be helpful to elucidate the effects of occlusion, iontophoresis, and other methods of augmenting delivery on the efficacy and side effects of topical anesthetics.[40] Additional randomized controlled trials examining the effectiveness of topical anesthesia for dermatologic procedures are also needed.

Pregnancy and lactation

There are currently no data available relevant to the clinical questions formulated on the use of topical anesthesia in pregnant or nursing women. Animal studies have revealed no evidence of harm to the fetus with infiltrated lidocaine.[22] Based on these reports, the US Food and Drug Administration rates lidocaine as a pregnancy category B medication, and based on this and other evidence, it is considered safe in small amounts for local injection during pregnancy.[22-24] No adverse effects were observed in infants of mothers breastfeeding after epidural anesthesia with lidocaine, and the American Academy of Pediatrics classifies lidocaine as compatible with lactation.[25,41] While data regarding the safety of topical anesthetic use in pregnancy are lacking, the authors recognize that the potential to conduct further studies in this population is limited by ethical constraints. Evidence supports the use of infiltrated lidocaine, and the serum levels of even high concentrations of topical lidocaine in nonpregnant women are low,[24,34,35] and it is therefore this work group's opinion that the drug is also safe for topical application on women who are pregnant or nursing. During pregnancy it is recommended that the medication be reserved for procedures of urgent medical necessity, and those that are not urgent should be postponed until after delivery or delayed until the second trimester when possible (to ensure that fetal organogenesis is complete). There are no data available on the safety of agents other than lidocaine, and their use during pregnancy and lactation is not recommended.

Use in children

Topical anesthetics are considered safe for use in children when dosed properly. The risk of toxicity, although rare, is increased by differences in children's body surface area (BSA) relative to weight and by a lack of linear relationship between BSA and drug exposure or response.[42] Potential adverse effects include methemoglobinemia with application of eutectic mixtures of lidocaine and prilocaine (equal mixtures of the 2 solid compounds by weight, which forms an oil above 18°C), and symptoms of local anesthetic systemic toxicity (LAST) described below, which may occur from any topical anesthetic. The recommendations for use provided in the package insert for each specific medication should be followed to avoid these complications.

Several investigations conducted in the emergency room have illustrated the effectiveness of topical anesthesia for laceration repair in the pediatric population.[19,26-31] A variety of agents and combinations are useful, although the addition of cocaine does not offer a clear benefit.[12,28,29,31] While studies in the dermatologic literature are sparse, the members of the work group routinely find that nonablative laser and other minor procedures (ie, curettage) may be performed in children under topical anesthesia. There are no studies comparing the utility of topical and infiltrative anesthesia for these procedures. The only head-to-head trial of these methods found the eutectic mixture of lidocaine and prilocaine to control postoperative pain from inguinal herniotomy equally as well as infiltrated lidocaine.[43]

Because of the scarcity of available evidence, consideration was therefore given to the patient experience when developing recommendations for the use of anesthesia when performing minimally invasive procedures in children. The pain of administering infiltration anesthesia, coupled with the anxiety surrounding the injection, can often lead to significant discomfort for a child. In contrast, the application of topical anesthesia is a reassuring process that can minimize stress in this setting. As such, the use of topical anesthesia is encouraged as a first-line option when performing minimally invasive office-based procedures on children. In cases where topical agents alone are insufficient, the members of the work group agree that adjunctive use of topical anesthesia to lessen the discomfort of infiltrative anesthesia should be considered. When more extensive surgery is required, combination of the 2 methods may also be used in select patients to avoid the need for sedation or general anesthesia.[32,33] The gap in research in this important area calls for future randomized controlled trials to compare the efficacy of topical and combination of topical and infiltration anesthesia for office-based procedures in children.

LOCAL INFILTRATION ANESTHESIA

The recommendations for the use of local infiltrative anesthesia and the strength of evidence are listed in Table VI and Table VII, respectively.

Safety and efficacy

Local infiltrative anesthesia is commonly used for a wide variety of office-based dermatologic

Table VI. Recommendations for the use of local infiltrative anesthesia in dermatologic surgery

Infiltrative anesthesia is safe and recommended for office-based dermatologic procedures, including but not limited to obtaining a biopsy specimen, excision, wound closure, tissue rearrangement, skin grafting, cauterization, nonablative laser, and ablative skin resurfacing
Infiltrative anesthesia may be combined with other forms of local anesthesia for larger or more complex cutaneous procedures, including but not limited to:
Full-face ablative laser resurfacing, combined with topical and nerve block anesthesia
Follicular unit hair transplantation, combined with tumescent local anesthesia
The maximum safe dose of local infiltrated anesthesia is unknown
For adults, no more than 4.5 mg/kg of lidocaine and 7.0 mg/kg of lidocaine with epinephrine should be administered in a single treatment
For children, no more than 1.5-2.0 mg/kg of lidocaine and 3.0-4.5 mg/kg of lidocaine with epinephrine should be administered in a single treatment
For a multistage procedure, such as Mohs micrographic surgery, a maximum dose of local infiltrative anesthesia of 50 mL of 1% lidocaine solution (500 mg) delivered over several hours is recommended
Use of either ester-type local anesthetics, bacteriostatic normal saline, or 1% diphenhydramine is suggested as an alternate form of local infiltration anesthesia for patients with true allergy to lidocaine
Steps recommended to decrease the risk of local anesthetic systemic toxicity:
Use the lowest effective dose of local anesthetic
Aspirate the needle/catheter prior to each injection to avoid introducing the drug directly into a vessel
Use incremental injections of anesthetic
Continually assess and communicate with the patient to monitor for signs of early toxicity

Table VII. Strength of recommendations for the use of local infiltrative anesthesia in dermatologic surgery

Recommendation	Strength of recommendation	Level of evidence	References
Use of local infiltrative anesthesia for obtaining a biopsy specimen, excision, wound closure, tissue rearrangement, skin grafting, cauterization, nonablative laser, and ablative skin resurfacing	C	III	Expert opinion
Combining methods of local anesthesia for full-face ablative laser and follicular unit hair transplantation	C	III	Expert opinion
Maximum dose of 4.5 mg/kg of lidocaine and 7.0 mg/kg of lidocaine with epinephrine for adults	C	III	3,44,45
Maximum dose of 1.5-2.0 mg/kg of lidocaine and 3.0-4.5 mg/kg of lidocaine with epinephrine	C	III	3
Max dose of 500 mg of lidocaine for a multistage Mohs micrographic surgery	B	II	46
Use of ester type local anesthetics for patients with lidocaine allergy	C	III	47
Use of diphenhydramine for patients with lidocaine allergy	C	III	48,49
Use of bacteriostatic normal saline for patients with lidocaine allergy	C	III	50
Prevention of local anesthetic systemic toxicity	A	I, II	51-53

procedures, and adverse events from medications delivered in this manner are rarely reported. There are no comparative studies to suggest that infiltrative anesthesia is safer than any other type of local anesthesia, and the work group considers topical, infiltrative, local nerve block, and tumescent local anesthesia all to be safe for use in the office-based setting. Based on clinical experience, procedures including but not limited to skin biopsy, excision, wound closure, tissue rearrangement, skin grafting, cauterization, nonablative laser, and ablative laser resurfacing may all be successfully performed under local infiltrative anesthesia. There are also no data to suggest that infiltrative anesthesia is more effective than other forms of local anesthesia. The only comparative study found regional nerve block and

local infiltration anesthesia to have equal efficacy in ptosis surgery, according to patient satisfaction with anesthesia.[54] The work group also finds it safe and effective to combine methods of local anesthesia for certain dermatologic procedures in order to prolong anesthesia, increase tolerability, or to minimize adverse effects of higher quantity of one agent. Infiltrative, topical, and local nerve block anesthesia together is a helpful combination for larger or more complex cutaneous procedures, such as full-face ablative laser resurfacing or Mohs micrographic surgery (MMS). Tumescent local anesthesia and infiltrative anesthesia are also useful in adjunct when preparing the recipient site for follicular unit hair transplantation.

Allergy to lidocaine is rare, with a genuine immunologic reaction representing only 1% of all adverse reactions to these medications.[47,55,56] For patients with a true allergy to lidocaine, one option is to switch to an ester type of local anesthetic, given that cross-reaction between both types is rare and usually attributed to paraben allergy in preservative-containing amide preparations or cosensitization.[47] Injection of 1% diphenhydramine has been also suggested, although it has a longer onset of action (5 min vs. 1 min for lidocaine) and limited efficacy.[48,49] Bacteriostatic saline (0.9% benzyl alcohol in normal saline) is another alternative, and 1 study suggests that injection of this agent with epinephrine may be less painful than injection of diphenhydramine.[50] Based on experience of the work group, injection of diphenhydramine or bacteriostatic normal saline may be useful as an anesthetic for small excisions and biopsies in patients with sensitivity or allergy to lidocaine.

Dosing

The maximum safe dose of local infiltrative anesthesia is unknown. Manufacturer recommended maximum doses of 7 mg/kg of lidocaine with epinephrine and 4.5 mg/kg of lidocaine without epinephrine appear safe for local infiltration in adults. Doses of 3.0 to 4.5 mg/kg of lidocaine with epinephrine and 1.5 to 2.0 mg/kg of lidocaine without epinephrine appear to be safe in children.[3] Expert opinion and clinical experience support the safety of these doses, but no published evidence exists to support these maximum limits.[44,45] Tumescent local anesthesia is a specialized form of local anesthesia, and its uses and safety are addressed later in this Guideline. A total lidocaine dose of 55 mg/kg has been found to be safe for office-based liposuction using tumescent local anesthesia.

There are also no studies examining the impact that incremental dosing over an extended time period has on the maximum safe amount of infiltrative anesthesia. A single prospective cohort study found a total dose of 50 mL of 1% lidocaine (500 mg) delivered in multiple increments over an average of 8 hours to be safe in MMS.[46] No signs of toxicity were observed, and serum lidocaine values did not approach toxic levels. Further investigation into the safety of local infiltration anesthesia when delivered incrementally over time may be helpful for planning lengthy or extensive office-based procedures.

Toxicity monitoring and prevention

Although there is great interpatient variability in the manifestations of LAST, the signs and symptoms tend to follow a progression of central nervous system excitement. The patient may initially experience circumoral numbness, facial tingling, pressured or slurred speech, metallic taste, auditory changes, and hallucinations, which may also be accompanied by hypertension and tachycardia. As the condition evolves, seizures or central nervous system depression may develop, and severe cases may end in cardiac failure or arrest.[51] The dose of local anesthesia needed for most dermatologic procedures is well below the manufacturer-recommended maximum, and anesthetic toxicity in the dermatologic setting is extremely rare. In addition, a new, easy-to-remember formula to calculate the maximum allowable volume of 2 of the most common local anesthetic agents used in dermatologic procedures may prevent any incidence of toxicity caused by errors in calculation.[57] As such, the treatment of LAST is beyond the scope of this guideline, although additional guidance can be sought in the literature.[52] Clinicians should be mindful of the potential for toxicity, however, and take the steps listed in Table VI to ensure patient safety.[51-53] Use of ultrasonographic guidance and intravascular markers have been suggested as additional precautions in order to avoid introducing the drug directly into a vessel.[51-53] This work group agrees that these methods may be considered but are not practical for everyday use by most dermatologists.

Addition of epinephrine

The recommendations for mixing and the use of additives to local infiltration anesthesia and the strength of evidence are listed in Tables VIII and IX, respectively.

Vasoconstrictors play an important role in providing optimal local anesthesia in dermatologic surgery by slowing mobilization of the anesthetic and thereby prolonging its effect, reducing peak blood levels, and providing hemostasis. Epinephrine (adrenaline) is the most common vasoconstrictor

Table VIII. Recommendations for mixing and the use of additives to local infiltrative anesthesia in dermatologic surgery

Epinephrine
The addition of epinephrine to local infiltration anesthesia is safe and recommended for use on the ear, nose, hand, feet, and digits
The addition of epinephrine to local infiltration anesthesia may be considered for use during procedures on the penis
Local infiltrative anesthesia with epinephrine may be used in small amounts in women who are pregnant:
Elective procedures and those not of urgent medical necessity requiring lidocaine with epinephrine should be postponed until after delivery
Procedures of urgent medical necessity should be delayed until the second trimester when possible
In case of doubt, consult with the patient's obstetrician
Local infiltrative anesthesia with epinephrine may be administered to patients with stable cardiac disease. If uncertain of a patient's ability to tolerate epinephrine, consult with the patient's cardiologist
Use of the lowest effective concentration of epinephrine to provide pain control and vasoconstriction in local infiltrative anesthesia is recommended
Hyaluronidase
Hyaluronidase may be used as an additive to local infiltration anesthesia to ease diffusion and reduce contour distortion, yet there are insufficient data to support a recommendation for its routine use in dermatologic surgery
Hyaluronidase should not be administered to patients with a known bee venom allergy
Buffering
The addition of sodium bicarbonate to local anesthetic, particularly lidocaine with epinephrine, is recommended to decrease the pain of delivery by subcutaneous or intradermal infiltration
Preinjection of buffered lidocaine solution is suggested to reduce the pain of bupivacaine infiltration
Mixing local anesthetics
It is unclear whether mixing multiple anesthetics for local infiltration poses further benefit over use of a single agent

Table IX. Strength of recommendations for mixing and the use of additives to local infiltrative anesthesia in dermatologic surgery

Recommendation	Strength of recommendation	Level of evidence	References
Addition of epinephrine to local anesthesia on the ear, nose, and digits	A	I, II	58-68
Addition of epinephrine to local anesthesia on the penis	B	II	69
Addition of epinephrine to local anesthesia in women who are pregnant or nursing	B	II	22
Addition of epinephrine to local anesthesia in patients with stable cardiac disease	B	I, II	70,71
Addition of epinephrine to local infiltrative anesthesia at the lowest effective concentration	B	II, III	72-74
Against addition of hyaluronidase to local anesthesia in patients with bee venom allergy	B	II	75
Against use of hyaluronidase to reduce tissue distortion and improve undermining	C	III	76,77
Addition of sodium bicarbonate to reduce pain of local anesthetic infiltration	A	I, II	78-82
Preinjection of buffered lidocaine to reduce pain of bupivacaine injection	C	III	Expert opinion
Mixing multiple anesthetics for the same procedure	C	II	83-90

used in local anesthetics. Clinicians historically maintained the idea that using vasoconstrictors in areas of skin served by terminal vessels would lead to necrosis. Extensive research has since examined this issue, and there is sufficient evidence to refute this dogma. Multiple systematic reviews and randomized controlled trials have found the addition of epinephrine to local infiltrative anesthesia to be safe for use in

the digits, hands, and feet.[58-67] No cases of necrosis were reported, and the use of epinephrine resulted in less need for tourniquet plus faster onset and longer duration of anesthesia.[61,66,67] The addition of epinephrine to tumescent local anesthesia for ear and nose reconstruction also resulted in no anesthesia-related complications, and led to decreased operative time and need for electrocautery hemostasis.[68] Unlike other factors, such as excessive injection volume, burn from hot soaks, or excessive tourniquet pressure,[59] epinephrine affords many benefits without the risk of skin necrosis. As such, the authors recommend adding epinephrine to local anesthesia when cutaneous surgery is to be performed at these anatomic locations.

A single retrospective study examined the addition of epinephrine to anesthesia for local penile ring block during circumcision. Investigators did not observe any anesthetic-related complications.[69] Clinical experience of the panel has also been that epinephrine is safe for use in penile skin surgery. Studies are limited, and additional data would be helpful in strengthening this recommendation.

Epinephrine is rated as a pregnancy category C drug by the US Food and Drug Administration, but in small amounts appears safe for use with local infiltrative anesthesia in pregnant women.[22] One study suggested an increase in malformations when mothers were exposed to systemic epinephrine in the first trimester.[22] The alfa-adrenergic properties of epinephrine may cause vasoconstriction of placental blood vessels. When used in small amounts for dermatologic surgery, however, the local vasoconstriction afforded by epinephrine limits maternal blood level and placental transfer of lidocaine, and the benefits seem to outweigh the risks.[22] Despite this, clinicians should postpone nonemergent dermatologic surgery requiring local infiltration anesthesia until after delivery to avoid undue risk. If possible, urgent surgery should be delayed until at least the second trimester. In cases where large amounts of anesthesia are necessary, consultation with the patient's obstetrician may be helpful to assess the risk to benefit ratio of the procedure.

The safety of small amounts of local infiltrative anesthesia with epinephrine in patients with stable cardiac disease has been demonstrated in dental surgery.[70] Patients with stable, controlled cardiovascular conditions, including hypertension, ischemic heart disease, arrhythmia, chronic coronary disease, and heart transplantation, were able to tolerate intraoral infiltration of a variety of anesthetics (eg, lidocaine 2%, mepivacaine 2%, and prilocaine 2%) combined with epinephrine (ranging from 1:80,000 to 1:200,000) and felypressin at doses between 1.8 and 3.6 mL.[70,71] Similar studies have not been conducted in the dermatologic setting, where procedures may require between 1 and 50 mL of anesthetic solution. In the clinical experience of the panel, however, local infiltration anesthesia with epinephrine has been used safely for dermatologic procedures in patients with stable cardiovascular disease. Combining clinical experience with the data extrapolated from the dental literature, the work group recommends that epinephrine in small amounts is safe for dermatologic surgery in this population. If a patient's ability to safely undergo a procedure is in question because of cardiovascular disease, consultation with the patient's cardiologist is recommended.

The most commonly used concentrations of epinephrine in dermatologic surgery are 1:100,000 and 1:200,000. Addition of epinephrine in concentrations of 1:50,000, 1:100,000, and 1:200,000 were all shown to have the same effects on vasoconstriction, and may prolong the anesthetic duration of lidocaine and bupivacaine by approximately 200%.[72-74] Concentrations of 1:800,000 to 1:3,200,000 prolong the duration of anesthesia by approximately 100%, and, while data are conflicting, may offer less effective vasoconstriction than the aforementioned concentrations.[72,74] Although complications from epinephrine added to local anesthesia at these doses are rare, the clinical experience of the work group suggests that sensitivity to the drug varies, and symptoms of palpitations and anxiety may occur in some patients. The authors recommend using the lowest effective concentration of epinephrine for dermatologic procedures.[73,74]

Addition of hyaluronidase

Hyaluronidase may be added to infiltration anesthesia with the intent of enhancing diffusion of the anesthetic solution. The mixing of hyaluronidase and infiltrative anesthesia is safe as demonstrated by 1 controlled trial, and aside from hypersensitivity reactions, adverse events caused by the agent have not been cited.[75,91,92] Cross-reactivity between bee venom and hyaluronidase exists, and hyaluronidase should not be administered to patients with a history of bee sting allergy. When allergy to hyaluronidase is in question, prick testing may be used for confirmation.[75]

While used more commonly in other medical specialties, the benefits of hyaluronidase in dermatologic procedures remain unclear. Reports describing experience with mixing 7.2 IU of hyaluronidase with local anesthetic for various skin surgeries claim the drug helps minimize tissue

distortion during infiltration and enhances ease of tissue undermining while operating.[76,77] However, there are no data to support these assertions. Randomized trials evaluating the effects of adding hyaluronidase to local infiltration anesthesia are needed to support these observations, and no recommendations for or against its use in dermatologic surgery can be made at this time.

Addition of sodium bicarbonate

There are multiple well-designed randomized controlled trials showing that the addition of sodium bicarbonate to local anesthetic in order to raise the pH (known as buffering) decreases patient pain during drug delivery via subcutaneous or intradermal infiltration.[78-81] In these studies, approximately 2 out of 3 patients noted a 20% to 40% decrease in injection pain with the addition of sodium bicarbonate compared to plain lidocaine with epinephrine. Other confirmatory studies that did not find statistical significance were likely underpowered.[82] One nonconfirmatory study compared a solution of 0.1% lidocaine without bicarbonate to a solution of 1% lidocaine with bicarbonate.[93] This was not a relevant comparison, however, because there was a 10-fold difference in lidocaine concentrations between the 2 groups. While the addition of sodium bicarbonate to infiltration anesthesia has not been examined in the pediatric population, the authors find that buffering anesthetic also decreases injection pain in children.

Lidocaine and bupivacaine were the only drugs studied, and the work group does not recommend buffering of the latter, because precipitation of the anesthetic may lead to decreased efficacy. The concentrations of sodium bicarbonate varied from 10 to 100 mEq/L. Most solutions were prepared by mixing 8.4% sodium bicarbonate and 1% lidocaine with epinephrine in a 1:9 or 1:10 ratio by volume, and members of the work group find both proportions to be effective in practice. Uncertainty is held by many clinicians regarding the duration of time that such a solution will remain active once buffered, because a rise in pH will cause precipitation of epinephrine and decrease the potential for vasoconstriction. Investigators found the concentration of epinephrine to decrease by 25% per week after the addition of 100 mEq/L of sodium bicarbonate.[80] A follow-up study confirmed that buffered anesthetic solutions prepared 1 week before use caused nearly equal areas of anesthesia and vasoconstriction as solutions mixed the day of the procedure.[79] This evidence suggests that buffered solutions of 1% lidocaine with epinephrine may be prepared up to 1 week in advance of use.

Mixing local infiltration anesthetics

Mixing 2 (and sometimes more) local anesthetics to obtain an earlier onset and longer duration is not an uncommon practice, and multiple randomized controlled trials comparing mixtures of local anesthetics have been conducted in both the ophthalmologic and dermatologic settings.[83-90,94-96] The combinations studied include bupivacaine and lidocaine, bupivacaine and mepivacaine, and prilocaine and ropivacaine. The clinical methodologies used and the conclusions drawn vary, but evidence suggests that mixing these agents for local infiltration and nerve block anesthesia is safe and effective. There are insufficient data to determine whether any combination results in a faster onset or longer duration of anesthesia, and no strong evidence supports the benefits of mixing anesthetics over the use of a single agent. The decision of when and how to use a mixture of drugs therefore currently rests on the experience and comfort level of the clinician. Additional research into the utility of mixing local anesthetics is warranted.

Minimizing pain of administration

The recommendations for minimizing pain of administration of infiltrative anesthesia (besides adding bicarbonate) and alternate methods of analgesia and the strength of evidence are listed in Tables X and XI, respectively.

There are separate, single, randomized control trials with small sample sizes that support the efficacy of slow infiltration rate, vibrating the skin, use of a warm (40°C) solution, and cold air skin cooling to decrease the pain of local anesthetic injection in adults.[97-101] Expert clinical experience supports the data from these studies, and also finds these measures to be of comparable benefit for use in children. Additional confirmatory studies on the utility of these techniques are needed.

Of studies conducted to evaluate the difference in pain upon intradermal and subcutaneous infiltration of different local anesthetics, only 1 incorporated a sufficiently large sample size. The roster of compared anesthetics differed amongst the trials, as did the findings of which medication hurt least upon injection. Two smaller trials found etidocaine to elicit the most discomfort and lidocaine the least of the studied drugs.[112,113] A third much larger trial found a preparation of mepivacaine from 1 manufacturer to cause less pain than lidocaine, while a preparation of mepivacaine from a second manufacturer induced more pain.[114] Additional study would be helpful to ascertain the reasons behind the differences in these findings and to aid in formulating a concrete recommendation.

Table X. Recommendations for minimizing pain of administration of local infiltration anesthesia and alternate methods of analgesia in dermatologic surgery

Slow rate of infiltration, vibration of the skin, use of a warm solution, or cold air skin cooling should be considered to decrease the pain of local anesthetic injection
It is unclear whether pretreatment with ethyl chloride spray, preinjection with normal saline, or verbal distraction decreases the pain of local anesthetic infiltration
There is contradictory evidence regarding the effectiveness of ethyl chloride, and its use as a sole method for analgesia in dermatologic procedures should not be considered
Cold air skin cooling may be considered to reduce patient discomfort during nonablative laser therapy
Use of a skin-vibrating device may be considered to help decrease the pain of botulinum toxin injection

Table XI. Strength of recommendations for minimizing pain of administration of local infiltration anesthesia and alternate methods of analgesia in dermatologic surgery

Recommendation	Strength of recommendation	Level of evidence	References
Slow rate of infiltration, vibration of the skin, use of a warm solution, and cold air skin cooling are recommended to decrease the pain of local anesthetic injection	B	II	97-101
Pretreatment with ethyl chloride spray, preinjection with normal saline, or verbal distraction to decrease the pain of local anesthetic infiltration	C	III	Expert opinion, 102
Ethyl chloride as an analgesic for dermatologic procedures	C	III	103-108
Cold air skin cooling to reduce patient discomfort during nonablative laser therapy	B	II	109,110
Use of a skin-vibrating device to decrease the pain of botulinum toxin injection into glabellar rhytides	B	II	111

There are limited and contradictory data examining the use of ethyl chloride, ice, verbal distraction, or preinjection of normal saline to decrease the pain of administering local anesthesia. While experience with these modalities has been that they are safe to use, and it has been suggested that combination of some of these techniques may increase patient acceptance of pain,[102] there does not appear to be clinical consensus or widespread agreement as to the true effectiveness of these methods.

ALTERNATE METHODS OF ANALGESIA

In addition to anesthetic drugs, multiple other modalities are available to alleviate patient discomfort during dermatologic procedures. There is, however, a great deal of variability in the level of evidence to support these methods. There is contradictory evidence regarding the pain reduction potential of ethyl chloride, with some studies showing benefit, some finding no benefit, and 1 showing that no anesthetic was superior.[103-107] Many of these studies were not blinded because of infeasibility, and the interventions evaluated were difficult to compare to one another. In addition, all of the investigations of ethyl chloride were conducted to assess its use in venipuncture, venous cannulation, or skin prick testing, which are different from procedures performed by dermatologists. Because of conflicting evidence and a paucity of data, no recommendation for or against the use of ethyl chloride spray as a stand-alone method of analgesia to decrease the pain of different procedures for dermatologic surgery can be rendered. Additional high quality trials are needed. If considering ethyl chloride for analgesia before the use of energy-based devices, caution should be used because it is flammable. There is 1 reported case of unwanted ignition with laser therapy that caused a first-degree burn.[108]

Two prospective, nonrandomized studies support the utility of cold air skin cooling in reducing pain and discomfort associated with nonablative laser procedures on the face. The first found cold air skin cooling to be superior to ice gel analgesia, while the second concluded that pulsed-dye laser treatment was more comfortable with cold air than without, and that cooling was associated with fewer thermal side effects and only a slight decrease in clearing of facial telangiectasias.[109,110] Other studies showing the limitations of the technique found cold air to be inferior to nerve block for facial photodynamic therapy, and

Table XII. Recommendations for nerve blocks in dermatologic surgery

Regional cutaneous nerve block anesthesia is recommended for ablative laser resurfacing of the face and botulinum toxin injection of the palm
Nerve block should be considered as an alternative or in addition to infiltrative anesthesia for procedures on the face, hands, feet, and digits, and may provide the benefit of decreased tissue swelling/distortion, prolong anesthesia, and reduce postoperative discomfort for the patient

Table XIII. Strength of recommendations for nerve blocks in dermatologic surgery

Recommendation	Strength of recommendation	Level of evidence	References
Nerve block anesthesia for ablative laser resurfacing of the face, botulinum toxin injection of the palm, and upper lid ptosis surgery	B	II	54,118-120
Nerve block as an alternate to local infiltration anesthesia for dermatologic surgery on the face and digits	C	III	Expert opinion

the combination of cold air and nerve block was equal to nerve block alone for ablative laser resurfacing on the face.[115,116] In addition to the data presented, the experience of the work group finds that despite limited utility in ablative procedures, cold air skin cooling can be efficacious for use in nonablative laser therapy and may be considered when patient comfort is of concern.

Lastly, there is also evidence to support the use of vibration to reduce pain of skin injections. One randomized, controlled, split-face trial found a significant decrease in pain of botulinum toxin injection to glabellar rhytides with the use of a skin vibration device.[111] Vibration has also been shown to be effective for reducing pain of other injections, including those of local anesthetic in eyelid surgery and venipuncture in the pediatric emergency room.[101,117] It may be helpful to consider use of vibration for injections performed in the dermatologic setting, especially for children and anxious adults.

NERVE BLOCKS

The recommendations for nerve blocks and the strength of evidence are listed in Tables XII and XIII, respectively.

A majority of investigations into the utility of nerve block anesthesia have been conducted outside the realm of dermatology, with dental studies dominating. Research for use in dermatologic procedures has found the technique to be safe when performed in this setting. Neither nerve damage nor other major adverse events have been reported, and mild events were limited to hematoma formation and 1 case of pain at the site of ulnar nerve block, all of which were transient.[54,115,118-125]

A review of the literature finds a modicum of evidence demonstrating the effectiveness of nerve block anesthesia for specific indications compared to other forms of local anesthesia. One dermatologic study found nerve block to be superior to topical anesthesia for patient-perceived pain while undergoing laser surgery on the face.[120] Multiple investigators have noted the efficacy of wrist nerve block before botulinum toxin injection for palmar hyperhidrosis, with 1 finding it superior to skin cooling.[118,119] An additional study comparing nerve block to local infiltrative anesthesia for ptosis surgery showed an equal level of patient satisfaction with the 2 techniques, supporting the potential use of nerve blocks as a valid alternative for this procedure.[54] Lastly, regional nerve blocks have also been shown to effectively reduce pain in full-face photodynamic therapy for actinic keratosis, with 1 study finding the technique superior to skin cooling.[115,123,124]

Clinical experience has shown nerve block anesthesia to be effective in situations beyond those described in the literature. A digital block may induce less injection pain than local infiltration of the tip of a finger or toe, and may also achieve a longer duration of anesthesia, resulting in less postoperative discomfort for the patient. In other areas, such as the lip and eyelid, nerve blocks allow for surgery without the local tissue swelling and distortion inherent with local infiltrative anesthesia. This can facilitate more precise surgery, albeit with the loss of benefit provided from epinephrine as a vasoconstrictor when used locally. There is a gap

Table XIV. Recommendations for tumescent local anesthesia in dermatologic surgery

Lidocaine and prilocaine are both safe and recommended for use in tumescent local anesthesia for office-based liposuction. Bupivacaine is not recommended for this use
Use of prilocaine is not approved in the United States for this procedure as of the date of this publication.
The addition of epinephrine to lidocaine is recommended and safe for use in tumescent local anesthesia for liposuction
A maximum dose of 55 mg/kg of lidocaine with epinephrine has been shown to be safe and can be used for tumescent local anesthesia for liposuction in patients weighing 43.6-81.8 kg
The use of warm anesthetic solution and a slow infiltration rate is recommended to decrease patient discomfort during administration of tumescent local anesthesia

Table XV. Strength of recommendations for tumescent local anesthesia in dermatologic surgery

Recommendation	Strength of recommendation	Level of evidence	References
Lidocaine and prilocaine for use in tumescent local anesthesia for office-based liposuction	A	I, II	126-134
The addition of epinephrine to lidocaine for use in tumescent local anesthesia for liposuction	A	I, II	126-131
A maximum dose of 55 mg/kg of lidocaine with epinephrine for local tumescent anesthesia for liposuction	A	I	135
Use of a warm solution to decrease patient discomfort during administration of tumescent local anesthesia	B	II	98
Use of a slow infiltration rate to decrease patient discomfort during administration of tumescent local anesthesia	C	III	136

in research in these areas, however. To better define the role of the technique in dermatologic surgery, studies comparing nerve block and infiltrative anesthesia for procedures on the nose, cheeks, lips, eyelids, hands, feet, digits, and nails would be helpful.

TUMESCENT LOCAL ANESTHESIA

The recommendations for tumescent local anesthesia and the strength of evidence are listed in Tables XIV and XV, respectively.

Tumescent local anesthesia, which was developed by a dermatologist, uses the subcutaneous infiltration of large volumes of dilute anesthetic to produce swelling and firmness of the targeted areas.[126] There is substantial evidence to support the safety of tumescent local anesthesia when used for office-based liposuction. There are no reports of death associated with liposuction performed under tumescent local anesthesia by dermatologists, and multiple studies estimate the rate of serious adverse events to be 0.04% to 0.16%.[137-141] Lidocaine with epinephrine is the most commonly studied solution and has been shown to be effective at multiple concentrations.[126-131] A well conducted prospective study found local tumescent anesthesia with lidocaine doses of 55 mg/kg to be safe for use in office-based liposuction, and expert experience supports this finding.[135] This recommendation is valid only for the weight range studied (43.6-81.8 kg), and the safety of this dose on patients weighing outside this range has not been confirmed. Prilocaine is not approved in the United States for tumescent local anesthesia, but it is also safe and effective for this procedure.[132-134] A combination of lidocaine and prilocaine may reduce the risk of toxicity from either drug and might be favorable in cases where a large volume of tumescent local anesthesia is needed.[132] There are no data examining other anesthetics for use in tumescent local anesthesia, including bupivacaine, and therefore no recommendations can be rendered.

As discussed above (see local infiltration anesthesia, minimizing the pain of administration), the use of a warm (40°C) solution is associated with significantly less patient discomfort during anesthetic infiltration in tumescent local anesthesia.[98] A single retrospective study of data from 4 experienced surgeons suggests that a slower rate of infusion also causes less patient discomfort during anesthetic administration but has no effect on pain level during liposuction.[136] Additional trials with confirmatory data would help to strengthen the level of these recommendations.

GAPS IN RESEARCH

The most current and highest level of evidence was examined in order to create this guideline. This thorough appraisal of the literature has revealed several areas in which additional investigation is needed regarding the use of local anesthesia for dermatologic procedures. Although mention is made in the narrative above, the work group would like to place additional emphasis on gaps in research, which include but are not limited to: randomized controlled trials to compare topical anesthetic to infiltrative local anesthetic for minor dermatologic procedures in children and adults; studies examining the effect of occlusion and type of vehicle (ie, cream, gel, and ointment) on the safety and efficacy of topical anesthetics; randomized controlled trials to compare the pain of administration and anesthetic efficacy of infiltrative anesthesia versus regional nerve block for dermatologic surgery on the face, hands, feet, and digits; additional data on the maximum safe dosage of local infiltration anesthesia for large, multistage procedures, such as Mohs micrographic surgery; additional trials on effectiveness of techniques used to decrease the pain of administering infiltrative anesthesia, including methods of auditory and visual distraction in children; well-designed studies to determine the utility of combining different infiltrative anesthetics for the same procedure; randomized controlled trials to examine the benefits of adding hyaluronidase to local infiltrative anesthesia; and randomized controlled trials to examine the effect rate of infiltration has on patient discomfort during tumescent local anesthesia for liposuction. It is hoped that such gaps are closed to further optimize the use of local anesthesia for office-based dermatologic surgery.

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

The below information represents the authors disclosed relationships with industry. Relevant relationships requiring recusal for drafting of guideline recommendations and content were not noted for this guideline.

Murad Alam, MD, served as consultant for Amway Corporation, receiving honoraria, and as Principal Investigator (PI) for OptMed, receiving grants with no personal compensation received.

Bernard Cohen, MD, served on the Advisory Board of Sanofi-Aventis, receiving honoraria.

C. William Hanke, MD, received honoraria serving on the Advisory Board of Allergan, Inc, as consultant for Orlando Dermatology Aesthetic & Clinical, as speaker for LEO Pharma and Genentech, Inc, and in other roles for Educational Testing and Assessment Systems, Inc and for Sanova Works. In addition, Dr Hanke served as PI in grants funded by Allergan, Inc, Derm Advance, Genentech, Inc, and LEO Pharma, and received compensation for patent royalties or other compensation for intellectual property rights from Elsevier, Informa HealthCare, and Springer Science & Business Media.

Neelam Vashi, MD, served as a consultant to L'Oreal, receiving honoraria.

Trudy Adamson, Jeremy Burdeaux, MD, MPH, Nathaniel Jellinek, MD, David Kouba, MD, PhD, Matteo LoPiccolo, MD, Howard Maibach, MD, Jose Moyano, PhD, and Wendy Smith Begolka, MBS have no relevant conflicts of interest to disclose.

REFERENCES

1. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004;17:59-67.
2. American Academy of Dermatology website. Administrative regulation — evidence-based clinical practice guidelines. Available at: https://www.aad.org/File%20Library/Global%20navigation/About%20the%20AAD/Administrative%20regulations/AR-evidence-based-clinical-practice-guidelines.pdf. Accessed February 3, 2016.
3. Hancox JG, Venkat AP, Hill A, et al. Why are there differences in the perceived safety of office-based surgery? *Dermatol Surg*. 2004;30:1377-1379.
4. Starling J 3rd, Thosani MK, Coldiron BM. Determining the safety of office-based surgery: what 10 years of Florida data and 6 years of Alabama data reveal. *Dermatol Surg*. 2012;38:171-177.
5. Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology*. 2005;102:509-514.
6. Liem EB, Lin CM, Suleman MI, et al. Anesthetic requirement is increased in redheads. *Anesthesiology*. 2004;101:279-283.
7. Chua MV, Tsueda K, Doufas AG. Midazolam causes less sedation in volunteers with red hair. *Can J Anaesth*. 2004;51:25-30.
8. Sadhasivam S, Chidambaran V, Ngamprasertwong P, et al. Race and unequal burden of perioperative pain and opioid related adverse effects in children. *Pediatrics*. 2012;129:832-838.
9. Hruza G. Anesthesia. In: Bolognia JJ, Jorizzo JL, Rapini RP, eds. *Dermatology*. 2nd ed. Spain: Elsevier; 2009.
10. Huether MJ, Brodland DG. Local anesthetics. In: Wolverton S, ed. *Comprehensive dermatologic drug therapy*. Philadelphia: Elsevier; 2007.
11. Soriano TT, Breithaupt A, Chesnut C. Anesthesia and analgesia. In: Robinson JK, Hanke CW, Siegel DM, Fratila A, eds. *Surgery of the skin*. China: Elsevier; 2010.
12. Eidelman A, Weiss JM, Enu IK, Lau J, Carr DB. Comparative efficacy and costs of various topical anesthetics for repair of

dermal lacerations: a systematic review of randomized, controlled trials. *J Clin Anesth*. 2005;17:106-116.
13. Bryan HA, Alster TS. The S-Caine peel: a novel topical anesthetic for cutaneous laser surgery. *Dermatol Surg*. 2002; 28:999-1003.
14. Kilmer SL, Chotzen V, Zelickson BD, et al. Full-face laser resurfacing using a supplemented topical anesthesia protocol. *Arch Dermatol*. 2003;139:1279-1283.
15. Franchi M, Cromi A, Scarperi S, Gaudino F, Siesto G, Ghezzi F. Comparison between lidocaine-prilocaine cream (EMLA) and mepivacaine infiltration for pain relief during perineal repair after childbirth: a randomized trial. *Am J Obstet Gynecol*. 2009;201:186.e1-186.e5.
16. Jones TM, Nandapalan V. Manipulation of the fractured nose: a comparison of local infiltration anaesthesia and topical local anaesthesia. *Clin Otolaryngol Allied Sci*. 1999; 24:443-446.
17. Goodacre TE, Sanders R, Watts DA, Stoker M. Split skin grafting using topical local anaesthesia (EMLA): a comparison with infiltrated anaesthesia. *Br J Plast Surg*. 1988;41:533-538.
18. Russell GN, Desmond MJ, Fox MA. Local anesthesia for radial artery cannulation: a comparison of a lidocaine-prilocaine emulsion and lidocaine infiltration. *J Cardiothorac Anesth*. 1988;2:309-312.
19. Ferguson C, Loryman B, Body R. Best evidence topic report. Topical anaesthetic versus lidocaine infiltration to allow closure of skin wounds in children. *Emerg Med J*. 2005;22: 507-509.
20. Hallen A, Ljunghall K, Wallin J. Topical anaesthesia with local anaesthetic (lidocaine and prilocaine, EMLA) cream for cautery of genital warts. *Genitourin Med*. 1987;63:316-319.
21. Gupta AK, Sibbald RG. Eutectic lidocaine/prilocaine 5% cream and patch may provide satisfactory analgesia for excisional biopsy or curettage with electrosurgery of cutaneous lesions. A randomized, controlled, parallel group study. *J Am Acad Dermatol*. 1996;35:419-423.
22. Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation. *J Am Acad Dermatol*. 2014;70:401.e1-401.e14.
23. Gormley DE. Cutaneous surgery and the pregnant patient. *J Am Acad Dermatol*. 1990;23:269-279.
24. Richards KA, Stasko T. Dermatologic surgery and the pregnant patient. *Dermatol Surg*. 2002;28:248-256.
25. Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation. *J Am Acad Dermatol*. 2014;70:417.e1-417.e10.
26. Bonadio WA, Wagner V. Half-strength TAC topical anesthetic. For selected dermal lacerations. *Clin Pediatr*. 1988;27:495-498.
27. Hegenbarth MA, Altieri MF, Hawk WH, Greene A, Ochsenschlager DW, O'Donnell R. Comparison of topical tetracaine, adrenaline, and cocaine anesthesia with lidocaine infiltration for repair of lacerations in children. *Ann Emerg Med*. 1990;19:63-67.
28. Smith GA, Strausbaugh SD, Harbeck-Weber C, et al. Prilocaine-phenylephrine and bupivacaine-phenylephrine topical anesthetics compared with tetracaine-adrenaline-cocaine during repair of lacerations. *Am J Emerg Med*. 1998;16: 121-124.
29. Smith GA, Strausbaugh SD, Harbeck-Weber C, Shields BJ, Powers JD, Hackenberg D. Comparison of topical anesthetics without cocaine to tetracaine-adrenaline-cocaine and lidocaine infiltration during repair of lacerations: bupivacaine-norepinephrine is an effective new topical anesthetic agent. *Pediatrics*. 1996;97:301-307.
30. Smith SM, Barry RC. A comparison of three formulations of TAC (tetracaine, adrenalin, cocaine) for anesthesia of minor lacerations in children. *Pediatr Emerg Care*. 1990;6:266-270.
31. Zempsky WT, Karasic RB. EMLA versus TAC for topical anesthesia of extremity wounds in children. *Ann Emerg Med*. 1997;30:163-166.
32. Pierluisi GJ, Terndrup TE. Influence of topical anesthesia on the sedation of pediatric emergency department patients with lacerations. *Pediatr Emerg Care*. 1989;5:211-215.
33. Priestley S, Kelly AM, Chow L, Powell C, Williams A. Application of topical local anesthetic at triage reduces treatment time for children with lacerations: a randomized controlled trial. *Ann Emerg Med*. 2003;42:34-40.
34. Carruthers JA, Carruthers JD, Poirier J, Oliff HS, Mordaunt J, Schreiber WE. Safety of lidocaine 15% and prilocaine 5% topical ointment used as local anesthesia for intense pulsed light treatment. *Dermatol Surg*. 2010;36:1130-1137.
35. McCleskey PE, Patel SM, Mansalis KA, Elam AL, Kinsley TR. Serum lidocaine levels and cutaneous side effects after application of 23% lidocaine 7% tetracaine ointment to the face. *Dermatol Surg*. 2013;39:82-91.
36. Alster T. Review of lidocaine/tetracaine cream as a topical anesthetic for dermatologic laser procedures. *Pain Ther*. 2013;2:11-19.
37. Berkman S, MacGregor J, Alster T. Adverse effects of topical anesthetics for dermatologic procedures. *Expert Opin Drug Saf*. 2012;11:415-423.
38. Sobanko JF, Miller CJ, Alster TS. Topical anesthetics for dermatologic procedures: a review. *Dermatol Surg*. 2012;38: 709-721.
39. Friedman PM, Fogelman JP, Nouri K, Levine VJ, Ashinoff R. Comparative study of the efficacy of four topical anesthetics. *Dermatol Surg*. 1999;25:950-954.
40. Greenbaum SS, Bernstein EF. Comparison of iontophoresis of lidocaine with a eutectic mixture of lidocaine and prilocaine (EMLA) for topically administered local anesthesia. *J Dermatol Surg Oncol*. 1994;20:579-583.
41. Ward RM, Bates BA, Benitz WE, et al. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108: 776-789.
42. Cella M, Knibbe C, Danhof M, Della Pasqua O. What is the right dose for children? *Br J Clin Pharmacol*. 2010;70:597-603.
43. Usmani H, Pal Singh S, Quadir A, Chana RS. A comparison between EMLA cream application versus lidocaine infiltration for postoperative analgesia after inguinal herniotomy in children. *Reg Anesth Pain Med*. 2009;34:106-109.
44. Klein JA. Tumescent technique for local anesthesia improves safety in large-volume liposuction. *Plast Reconstr Surg*. 1993; 92:1085-1098. discussion 99-100.
45. Drake LA, Dinehart SM, Goltz RW, et al. Guidelines of care for local and regional anesthesia in cutaneous surgery. Guidelines/Outcomes Committee: American Academy of Dermatology. *J Am Acad Dermatol*. 1995;33:504-509.
46. Alam M, Ricci D, Havey J, Rademaker A, Witherspoon J, West DP. Safety of peak serum lidocaine concentration after Mohs micrographic surgery: a prospective cohort study. *J Am Acad Dermatol*. 2010;63:87-92.
47. Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. *Br J Anaesth*. 2012;108: 903-911.
48. Green SM, Rothrock SG, Gorchynski J. Validation of diphenhydramine as a dermal local anesthetic. *Ann Emerg Med*. 1994;23:1284-1289.

49. Xia Y, Chen E, Tibbits DL, Reilley TE, McSweeney TD. Comparison of effects of lidocaine hydrochloride, buffered lidocaine, diphenhydramine, and normal saline after intradermal injection. *J Clin Anesth*. 2002;14:339-343.
50. Bartfield JM, Jandreau SW, Raccio-Robak N. Randomized trial of diphenhydramine versus benzyl alcohol with epinephrine as an alternative to lidocaine local anesthesia. *Ann Emerg Med*. 1998;32:650-654.
51. Neal JM, Bernards CM, Butterworth JF 4th, et al. ASRA practice advisory on local anesthetic systemic toxicity. *Reg Anesth Pain Med*. 2010;35:152-161.
52. Neal JM, Mulroy MF, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. *Reg Anesth Pain Med*. 2012;37:16-18.
53. Mercado P, Weinberg GL. Local anesthetic systemic toxicity: prevention and treatment. *Anesthesiol Clin*. 2011;29:233-242.
54. Lee EJ, Khandwala M, Jones CA. A randomised controlled trial to compare patient satisfaction with two different types of local anaesthesia in ptosis surgery. *Orbit*. 2009;28:388-391.
55. Rood JP. Adverse reaction to dental local anaesthetic injection—'allergy' is not the cause. *Br Dent J*. 2000;189:380-384.
56. Jenerowicz D, Polanska A, Glinska O, Czarnecka-Operacz M, Schwartz RA. Allergy to lidocaine injections: comparison of patient history with skin testing in five patients. *Postepy Dermatol Alergol*. 2014;31:134-138.
57. Walsh K, Arya R. A simple formula for quick and accurate calculation of maximum allowable volume of local anaesthetic agents. *Br J Dermatol*. 2015;172:825-826.
58. Altinyazar HC, Ozdemir H, Koca R, Hosnuter M, Demirel CB, Gundogdu S. Epinephrine in digital block: color Doppler flow imaging. *Dermatol Surg*. 2004;30:508-511.
59. Chowdhry S, Seidenstricker L, Cooney DS, Hazani R, Wilhelmi BJ. Do not use epinephrine in digital blocks: myth or truth? Part II. A retrospective review of 1111 cases. *Plast Reconstr Surg*. 2010;126:2031-2034.
60. Denkler K. A comprehensive review of epinephrine in the finger: to do or not to do. *Plast Reconstr Surg*. 2001;108:114-124.
61. Denkler K. Dupuytren's fasciectomies in 60 consecutive digits using lidocaine with epinephrine and no tourniquet. *Plast Reconstr Surg*. 2005;115:802-810.
62. Hafner HM, Schmid U, Moehrle M, Strolin A, Breuninger H. Changes in acral blood flux under local application of ropivacaine and lidocaine with and without an adrenaline additive: a double-blind, randomized, placebo-controlled study. *Clin Hemorheol Microcirc*. 2008;38:279-288.
63. Krunic AL, Wang LC, Soltani K, Weitzul S, Taylor RS. Digital anesthesia with epinephrine: an old myth revisited. *J Am Acad Dermatol*. 2004;51:755-759.
64. Lalonde D, Bell M, Benoit P, Sparkes G, Denkler K, Chang P. A multicenter prospective study of 3,110 consecutive cases of elective epinephrine use in the fingers and hand: the Dalhousie Project clinical phase. *J Hand Surg*. 2005;30:1061-1067.
65. Radovic P, Smith RG, Shumway D. Revisiting epinephrine in foot surgery. *J Am Podiatr Med Assoc*. 2003;93:157-160.
66. Sonohata M, Nagamine S, Maeda K, et al. Subcutaneous single injection digital block with epinephrine. *Anesthesiol Res Pract*. 2012;2012:487650.
67. Wilhelmi BJ, Blackwell SJ, Miller JH, et al. Do not use epinephrine in digital blocks: myth or truth? *Plast Reconstr Surg*. 2001;107:393-397.
68. Hafner HM, Rocken M, Breuninger H. Epinephrine-supplemented local anesthetics for ear and nose surgery: clinical use without complications in more than 10,000 surgical procedures. *J Dtsch Dermatol Ges*. 2005;3:195-199.
69. Schnabl SM, Herrmann N, Wilder D, Breuninger H, Hafner HM. Clinical results for use of local anesthesia with epinephrine in penile nerve block. *J Dtsch Dermatol Ges*. 2014;12:332-339.
70. Serrera Figallo MA, Velazquez Cayon RT, Torres Lagares D, Corcuera Flores JR, Machuca Portillo G. Use of anesthetics associated to vasoconstrictors for dentistry in patients with cardiopathies. Review of the literature published in the last decade. *J Clin Exp Dent*. 2012;4:e107-e111.
71. Niwa H, Sugimura M, Satoh Y, Tanimoto A. Cardiovascular response to epinephrine-containing local anesthesia in patients with cardiovascular disease. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001;92:610-616.
72. Dunlevy TM, O'Malley TP, Postma GN. Optimal concentration of epinephrine for vasoconstriction in neck surgery. *Laryngoscope*. 1996;106:1412-1414.
73. Gessler EM, Hart AK, Dunlevy TM, Greinwald JH Jr. Optimal concentration of epinephrine for vasoconstriction in ear surgery. *Laryngoscope*. 2001;111:1687-1690.
74. Liu S, Carpenter RL, Chiu AA, McGill TJ, Mantell SA. Epinephrine prolongs duration of subcutaneous infiltration of local anesthesia in a dose-related manner. Correlation with magnitude of vasoconstriction. *Reg Anesth*. 1995;20:378-384.
75. Kirby B, Butt A, Morrison AM, Beck MH. Type I allergic reaction to hyaluronidase during ophthalmic surgery. *Contact Derm*. 2001;44:52.
76. Clark LE, Mellette JR Jr. The use of hyaluronidase as an adjunct to surgical procedures. *J Dermatol Surg Oncol*. 1994;20:842-844.
77. Landsman L, Mandy SH. Adjuncts to scalp reduction surgery. Intraoperative tissue expanders and hyaluronidase. *J Dermatol Surg Oncol*. 1991;17:670-672.
78. Masters JE. Randomised control trial of pH buffered lignocaine with adrenaline in outpatient operations. *Br J Plast Surg*. 1998;51:385-387.
79. Stewart JH, Chinn SE, Cole GW, Klein JA. Neutralized lidocaine with epinephrine for local anesthesia—II. *J Dermatol Surg Oncol*. 1990;16:842-845.
80. Stewart JH, Cole GW, Klein JA. Neutralized lidocaine with epinephrine for local anesthesia. *J Dermatol Surg Oncol*. 1989;15:1081-1083.
81. Welch MN, Czyz CN, Kalwerisky K, Holck DE, Mihora LD. Double-blind, bilateral pain comparison with simultaneous injection of 2% lidocaine versus buffered 2% lidocaine for periocular anesthesia. *Ophthalmology*. 2012;119:2048-2052.
82. Burns CA, Ferris G, Feng C, Cooper JZ, Brown MD. Decreasing the pain of local anesthesia: a prospective, double-blind comparison of buffered, premixed 1% lidocaine with epinephrine versus 1% lidocaine freshly mixed with epinephrine. *J Am Acad Dermatol*. 2006;54:128-131.
83. Gadsden J, Hadzic A, Gandhi K, et al. The effect of mixing 1.5% mepivacaine and 0.5% bupivacaine on duration of analgesia and latency of block onset in ultrasound-guided interscalene block. *Anesth Analg*. 2011;112:471-476.
84. Lai F, Sutton B, Nicholson G. Comparison of L-bupivacaine 0.75% and lidocaine 2% with bupivacaine 0.75% and lidocaine 2% for peribulbar anaesthesia. *Br J Anaesth*. 2003;90:512-514.
85. Nicholson G, Sutton B, Hall GM. Comparison of 1% ropivacaine with 0.75% bupivacaine and 2% lidocaine for peribulbar anaesthesia. *Br J Anaesth*. 2000;84:89-91.

86. Ozdemir M, Ozdemir G, Zencirci B, Oksuz H. Articaine versus lidocaine plus bupivacaine for peribulbar anaesthesia in cataract surgery. *Br J Anaesth*. 2004;92:231-234.
87. Ribotsky BM, Berkowitz KD, Montague JR. Local anesthetics. Is there an advantage to mixing solutions? *J Am Podiatr Med Assoc*. 1996;86:487-491.
88. Seow LT, Lips FJ, Cousins MJ, Mather LE. Lidocaine and bupivacaine mixtures for epidural blockade. *Anesthesiology*. 1982;56:177-183.
89. Sweet PT, Magee DA, Holland AJ. Duration of intradermal anaesthesia with mixtures of bupivacaine and lidocaine. *Can Anaesth Soc J*. 1982;29:481-483.
90. van den Berg AA, Montoya-Pelaez LF. Comparison of lignocaine 2% with adrenaline, bupivacaine 0.5% with or without hyaluronidase and a mixture of bupivacaine, lignocaine and hyaluronidase for peribulbar block analgesia. *Acta Anaesthesiol Scand*. 2001;45:961-966.
91. Wohlrab J, Finke R, Franke WG, Wohlrab A. Clinical trial for safety evaluation of hyaluronidase as diffusion enhancing adjuvant for infiltration analgesia of skin with lidocaine. *Dermatol Surg*. 2012;38:91-96.
92. Feighery C, McCoy EP, Johnston PB, Armstrong DK. Delayed hypersensitivity to hyaluronidase (Hyalase) used during cataract surgery. *Contact Derm*. 2007;57:343.
93. Zaiac M, Aguilera SB, Zaulyanov-Scanlan L, Caperton C, Chimento S. Virtually painless local anesthesia: diluted lidocaine proves to be superior to buffered lidocaine for subcutaneous infiltration. *J Drugs Dermatol*. 2012;11:e39-e42.
94. Allman KG, Barker LL, Werrett GC, Gouws P, Sturrock GD, Wilson IH. Comparison of articaine and bupivacaine/lidocaine for peribulbar anaesthesia by inferotemporal injection. *Br J Anaesth*. 2002;88:676-678.
95. Breuninger H, Schimek F, Heeg P. Subcutaneous infusion anesthesia with diluted mixtures of prilocain and ropivacain. *Langenbecks Arch Surg*. 2000;385:284-289.
96. Dopfmer UR, Maloney DG, Gaynor PA, Ratcliffe RM, Dopfmer S. Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia. *Br J Anaesth*. 1996;76:77-80.
97. Fosko SW, Gibney MD, Harrison B. Repetitive pinching of the skin during lidocaine infiltration reduces patient discomfort. *J Am Acad Dermatol*. 1998;39:74-78.
98. Kaplan B, Moy RL. Comparison of room temperature and warmed local anesthetic solution for tumescent liposuction. A randomized double-blind study. *Dermatol Surg*. 1996;22:707-709.
99. Scarfone RJ, Jasani M, Gracely EJ. Pain of local anesthetics: rate of administration and buffering. *Ann Emerg Med*. 1998;31:36-40.
100. Al-Qarqaz F, Al-Aboosi M, Al-shiyab D, Al Dabbagh Z. Using cold air for reducing needle-injection pain. *Int J Dermatol*. 2012;51:848-852.
101. Fayers T, Morris DS, Dolman PJ. Vibration-assisted anesthesia in eyelid surgery. *Ophthalmology*. 2010;117:1453-1457.
102. Swinehart JM. The ice-saline-Xylocaine technique. A simple method for minimizing pain in obtaining local anesthesia. *J Dermatol Surg Oncol*. 1992;18:28-30.
103. Armstrong P, Young C, McKeown D. Ethyl chloride and venepuncture pain: a comparison with intradermal lidocaine. *Can J Anaesth*. 1990;37:656-658.
104. Robinson PA, Carr S, Pearson S, Frampton C. Lignocaine is a better analgesic than either ethyl chloride or nitrous oxide for peripheral intravenous cannulation. *Emerg Med Australas*. 2007;19:427-432.
105. Selby IR, Bowles BJ. Analgesia for venous cannulation: a comparison of EMLA (5 minutes application), lignocaine, ethyl chloride, and nothing. *J Royal Soc Med*. 1995;88:264-267.
106. Soueid A, Richard B. Ethyl chloride as a cryoanalgesic in pediatrics for venipuncture. *Pediatr Emerg Care*. 2007;23:380-383.
107. Yoon WY, Chung SP, Lee HS, Park YS. Analgesic pretreatment for antibiotic skin test: vapocoolant spray vs ice cube. *Am J Emerg Med*. 2008;26:59-61.
108. White JM, Siegfried E, Boulden M, Padda G. Possible hazards of cryogen use with pulsed dye laser. A case report and summary. *Dermatol Surg*. 1999;25:250-252; discussion 252-253.
109. Hammes S, Raulin C. Evaluation of different temperatures in cold air cooling with pulsed-dye laser treatment of facial telangiectasia. *Lasers Surg Med*. 2005;36:136-140.
110. Raulin C, Greve B, Hammes S. Cold air in laser therapy: first experiences with a new cooling system. *Lasers Surg Med*. 2000;27:404-410.
111. Sharma P, Czyz CN, Wulc AE. Investigating the efficacy of vibration anesthesia to reduce pain from cosmetic botulinum toxin injections. *Aesthet Surg J*. 2011;31:966-971.
112. Howe NR, Williams JM. Pain of injection and duration of anesthesia for intradermal infiltration of lidocaine, bupivacaine, and etidocaine. *J Dermatol Surg Oncol*. 1994;20:459-464.
113. Morris R, McKay W, Mushlin P. Comparison of pain associated with intradermal and subcutaneous infiltration with various local anesthetic solutions. *Anesth Analg*. 1987;66:1180-1182.
114. Prien T. Intradermal anaesthesia: comparison of several compounds. *Acta Anaesth Scand*. 1994;38:805-807.
115. Serra-Guillen C, Hueso L, Nagore E, et al. Comparative study between cold air analgesia and supraorbital and supratrochlear nerve block for the management of pain during photodynamic therapy for actinic keratoses of the frontotemporal zone. *Br J Dermatol*. 2009;161:353-356.
116. Tierney EP, Hanke CW. The effect of cold-air anesthesia during fractionated carbon-dioxide laser treatment: prospective study and review of the literature. *J Am Acad Dermatol*. 2012;67:436-445.
117. Baxter AL, Cohen LL, McElvery HL, Lawson ML, von Baeyer CL. An integration of vibration and cold relieves venipuncture pain in a pediatric emergency department. *Pediatr Emerg Care*. 2011;27:1151-1156.
118. Hund M, Rickert S, Kinkelin I, Naumann M, Hamm H. Does wrist nerve block influence the result of botulinum toxin A treatment in palmar hyperhidrosis? *J Am Acad Dermatol*. 2004;50:61-62.
119. Vadoud-Seyedi J, Heenen M, Simonart T. Treatment of idiopathic palmar hyperhidrosis with botulinum toxin. Report of 23 cases and review of the literature. *Dermatology*. 2001;203:318-321.
120. Wan K, Jing Q, Sun QN, et al. Application of a peripheral nerve block technique in laser treatment of the entire facial skin and evaluation of its analgesic effect. *Eur J Dermatol*. 2013;23:324-330.
121. Altinyazar HC, Demirel CB, Koca R, Hosnuter M. Digital block with and without epinephrine during chemical matricectomy with phenol. *Dermatol Surg*. 2010;36:1568-1571.
122. Fujita M, Mann T, Mann O, Berg D. Surgical pearl: use of nerve blocks for botulinum toxin treatment of palmar-plantar hyperhidrosis. *J Am Acad Dermatol*. 2001;45:587-589.
123. Halldin CB, Paoli J, Sandberg C, Gonzalez H, Wennberg AM. Nerve blocks enable adequate pain relief during topical photodynamic therapy of field cancerization on the forehead and scalp. *Br J Dermatol*. 2009;160:795-800.

124. Paoli J, Halldin C, Ericson MB, Wennberg AM. Nerve blocks provide effective pain relief during topical photodynamic therapy for extensive facial actinic keratoses. *Clin Exp Dermatol*. 2008;33:559-564.
125. Thomson CJ, Lalonde DH. Randomized double-blind comparison of duration of anesthesia among three commonly used agents in digital nerve block. *Plast Reconstr Surg*. 2006; 118:429-432.
126. Klein JA. Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction. *J Dermatol Surg Oncol*. 1990;16:248-263.
127. Burk RW 3rd, Guzman-Stein G, Vasconez LO. Lidocaine and epinephrine levels in tumescent technique liposuction. *Plast Reconstr Surg*. 1996;97:1379-1384.
128. Glowacka K, Orzechowska-Juzwenko K, Bieniek A, Wiela-Hojenska A, Hurkacz M. Optimization of lidocaine application in tumescent local anesthesia. *Pharmacol Rep*. 2009;61:641-653.
129. Habbema L. Efficacy of tumescent local anesthesia with variable lidocaine concentration in 3430 consecutive cases of liposuction. *J Am Acad Dermatol*. 2010;62:988-994.
130. Lillis PJ. Liposuction surgery under local anesthesia: limited blood loss and minimal lidocaine absorption. *J Dermatol Surg Oncol*. 1988;14:1145-1148.
131. Rubin JP, Bierman C, Rosow CE, et al. The tumescent technique: the effect of high tissue pressure and dilute epinephrine on absorption of lidocaine. *Plast Reconstr Surg*. 1999;103:990-996; discussion 997-1002.
132. 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;221:248-252.
133. Breuninger H, Wehner-Caroli J. Slow infusion tumescent anesthesia. *Dermatol Surg*. 1998;24:759-763.
134. Lindenblatt N, Belusa L, Tiefenbach B, Schareck W, Olbrisch RR. Prilocaine plasma levels and methemoglobinemia in patients undergoing tumescent liposuction involving less than 2,000 ml. *Aesthetic Plast Surg*. 2004;28:435-440.
135. Ostad A, Kageyama N, Moy RL. Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction. *Dermatol Surg*. 1996;22:921-927.
136. Hanke CW, Coleman WP 3rd, Lillis PJ, et al. Infusion rates and levels of premedication in tumescent liposuction. *Dermatol Surg*. 1997;23:1131-1134.
137. Bernstein G, Hanke CW. Safety of liposuction: a review of 9478 cases performed by dermatologists. *J Dermatol Surg Oncol*. 1988;14:1112-1114.
138. Boeni R. Safety of tumescent liposuction under local anesthesia in a series of 4,380 patients. *Dermatology*. 2011;222: 278-281.
139. Hanke W, Cox SE, Kuznets N, Coleman WP 3rd. Tumescent liposuction report performance measurement initiative: national survey results. *Dermatol Surg*. 2004;30:967-977. discussion 78.
140. Housman TS, Lawrence N, Mellen BG, et al. The safety of liposuction: results of a national survey. *Dermatol Surg*. 2002; 28:971-978.
141. Hanke CW, Bullock S, Bernstein G. Current status of tumescent liposuction in the United States. National survey results. *Dermatol Surg*. 1996;22:595-598.