Parameters in fractional laser assisted delivery of topical anesthetics: A randomized controlled study on the role of the anesthetic and application time

To the Editor: Local anesthesia is frequently used before dermatologic surgical or laser procedures, including fractional or full-surface resurfacing procedures. Injectable anesthetics are effective but uncomfortable during administration. Topical application of anesthetics is time consuming and often only partial anesthesia is achieved because of the barrier function of the stratum corneum.[1] Ablative fractional laser (AFXL) pretreatment enhances penetration of topical anesthetics, but the optimal anesthetic drug and application time in this technique are unknown.[2,3] The aim of this study was to compare the efficacy of 2 different commercially available local anesthetics on AFXL-pretreated skin, articaine hydrochloride 40 mg/mL plus epinephrine 10 μg/mL solution (AHES, Ultracain D-S forte; Sanofi-Aventis, Paris, France; 4% anesthetic) and lidocaine 70 mg/g plus tetracaine 70 mg/g cream (LTC; Pliaglis, Galderma, Lausanne, Switzerland; 14% anesthetic), and to assess the role of the application time.

In 15 healthy volunteers (mean age 25.9 years), 6 10- × 10-mm regions on the back were pretreated with a fractional CO_2 laser (Ultrapulse, DeepFx, Lumenis Inc., Santa Clara, CA; 2.5 mJ, 75-μm channel depth, ±120 μm width, 15% density) followed by application of AHES or LTC for 5, 15, or 25 minutes (Fig 1). Subsequently, a CO_2 laser pain stimulus (50 mJ, 1500 μm channel depth, 5% density) was given to each region and to unanesthetized skin as a reference. Pain was scored on a 0 to 10 visual analog scale (VAS). The sample size was calculated to be able to detect a significant difference of 1 point on the VAS, which is thought to be the cutoff for clinical relevance.[4]

Pretreatment was well tolerated by all subjects (median VAS score 2.4). Median VAS scores were significantly lower for all test regions compared to unanesthetized skin (2.50 [AHES 5 minutes], 0.43 [AHES 15 minutes], 0.07 [AHES 25 minutes], 4.21 [LTC 5 minutes], 3.21 [LTC 15 minutes], and 3.14 [LTC 25 minutes] vs 4.71 [unanesthetized skin]) and for AHES versus LTC ($P < .01$; Fig 2). VAS scores were significantly lower for the AHES 25-minute and AHES 15-minute groups versus the AHES 5-minute group ($P < .01$) but not for the AHES 25-minute group versus the AHES 15-minute group ($P = .142$), possibly indicating that a state of saturation might have been achieved after 15 minutes (for the selected parameters). Application time did not influence VAS scores for the LTC regions ($P = .160$).

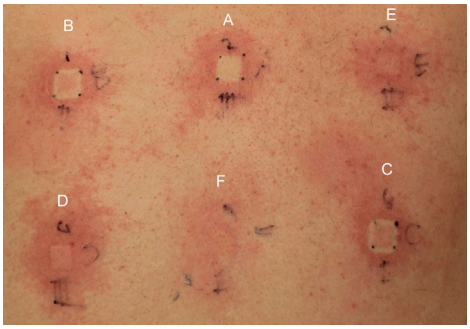

Fig 1. The back of one of the subjects after removal of the anesthetics. **A**, Articaine hydrochloride 40 mg/mL and epinephrine 10 μg/mL solution (AHES), 5-minute application time. **B**, AHES, 15-minute application time. **C**, AHES, 25-minute application time. **D**, Lidocaine 70 mg/g and tetracaine 70 mg/g cream (LTC), 5-minute application time. **E**, LTC, 15-minute application time. **F**, LTC, 25-minute application time. Note the evident epinephrine-induced vasoconstriction in the test regions treated with AHES.

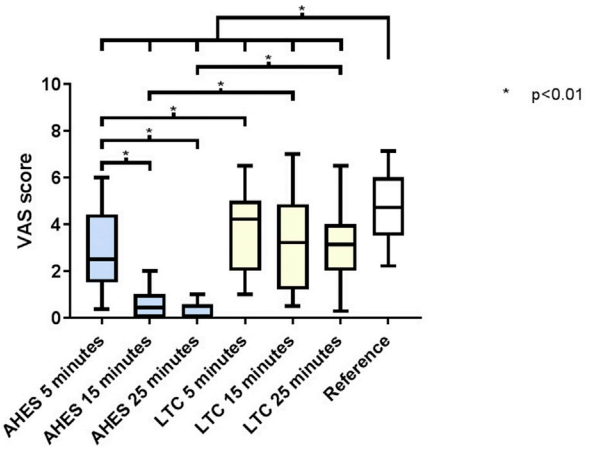

Fig 2. Boxplots showing the median and range of visual analog scale (VAS) scores after the pain stimulus. VAS scores for all test regions were significantly lower compared to the reference pain stimulus on unanesthetized skin and for the test regions treated with articaine hydrochloride 40 mg/mL and epinephrine 10 μg/mL solution (AHES) compared with the corresponding region treated with lidocaine 70 mg/g and tetracaine 70 mg/g cream (LTC) ($P < .01$). VAS scores were significantly lower for the AHES 25-minute and AHES 15-minute groups than for the AHES 5-minute group ($P < .01$) but were not significantly different between the AHES 25-minute and AHES 15-minute groups ($P = .142$). There were no significant differences between the LTC 5-minute, LTC 15-minute, and LTC 25-minute groups ($P = .160$).

In a previous pilot study, we showed that AHES was more effective than a 5% lidocaine/prilocaine

cream on AFXL-pretreated skin.[5] Since concentration of anesthetics was comparable for both formulations (AHES 4% vs lidocaine/prilocaine 5%), we proposed that a liquid solution may penetrate more easily into the AFXL ablation channels. Therefore, in the present study we aimed to compare AHES with a cream formulation containing a much higher concentration of anesthetics (AHES 4% vs LTC 14%), which may still not have sufficiently compensated for the possibly inferior vehicle. Despite the lack of comparability of the pharmacologic properties of both anesthetics (different anesthetics, presence of the potent vasoconstrictor epinephrine in AHES, which could enhance the sustained effect of the anesthetic), our finding that AHES still rendered more effective anesthesia than LTC might be considered as another indication for the superiority of a liquid vehicle.

In conclusion, both AHES and LTC give effective anesthesia when applied on AFXL-pretreated skin for ≥5 minutes. Maximum anesthesia is already achieved after 15 minutes for AHES. Despite the much lower concentration of anesthetic, AHES is superior to LTC in this setting. Additional research comparing different formulations containing the same anesthetic at a fixed concentration is needed to assess the exact role of the drug vehicle in AFXL-assisted topical anesthesia and drug delivery in general.

Arne A. Meesters, MD,[a,b] Marilin J. Nieboer, MD,[a] Menno A. de Rie, MD, PhD,[b,c] and Albert Wolkerstorfer, MD, PhD[a,b]

Netherlands Institute for Pigment Disorders,[a] Department of Dermatology,[b] Academic Medical Center, University of Amsterdam, and the Department of Dermatology,[c] VU Medical Center, VU University, Amsterdam, The Netherlands

Funding sources: None.

Conflicts of interest: None disclosed.

Approved by the Institutional Review Board of the Academic Medical Center, University of Amsterdam. ClinicalTrials.gov identifier NCT03279757.

Reprint requests: Arne A. Meesters, MD, Netherlands Institute for Pigment Disorders, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

E-mail: a.a.meesters@amc.uva.nl

REFERENCES

1. Manuskiatti W, Triwongwaranat D, Varothai S, Eimpunth S, Wanitphakdeedecha R. Efficacy and safety of a carbon-dioxide ablative fractional resurfacing device for treatment of atrophic acne scars in Asians. *J Am Acad Dermatol*. 2010;63:274-283.
2. Bachhav YG, Summer S, Heinrich A, et al. Effect of controlled laser microporation on drug transport kinetics into and across the skin. *J Control Release*. 2010;146:31-36.
3. Oni G, Rasko Y, Kenkel J. Topical lidocaine enhanced by laser pretreatment: a safe and effective method of analgesia for facial rejuvenation. *Aesthet Surg J*. 2013;33:854-861.
4. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? *Acad Emerg Med*. 1998;5:1086-1090.
5. Meesters AA, Bakker MM, de Rie MA, Wolkerstorfer A. Fractional CO2 laser assisted delivery of topical anesthetics: a randomized controlled pilot study. *Lasers Surg Med*. 2016;48:208-211.

https://doi.org/10.1016/j.jaad.2018.08.013

Predominance of oral mucosal melanoma in areas of high mechanical stress

To the Editor: Melanoma uncommonly involves the oral cavity and pursues an aggressive course with poor prognosis in this anatomic location. The risk factors of primary oral mucosal melanoma (POMM) are unknown and, unlike cutaneous melanoma, do not include sun exposure. The prognosis of this melanoma variant is likely associated with late detection and inadequate screening. Previous POMM case reports have shown that the oral cavity is not uniformly affected but rather shows striking predilection for the hard palatal mucosa and maxillary gingiva.[1] In contrast, squamous cell carcinoma, comprising 90% of oral cavity malignancies, has a predilection for the ventrolateral aspect of the tongue, the floor of the mouth, and gingiva and rarely involves the hard palatal mucosa.[2,3] As with POMM pathogenesis, the reason for its unique predilection remains unclear. These questions prompted a systematic review of POMM cases to establish a comprehensive anatomic predilection that may educate dermatologists on the importance of screening areas of the oral cavity, provide insight into novel candidate risk factors for POMM, and raise awareness of this melanoma presentation to clinicians.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used to search MEDLINE, Embase, and the Cochrane database for POMM cases with specific anatomic location stated. Twenty-one retrospective cohort studies and 4 case series totaling 549 POMM cases met the inclusion criteria. The maxillary gingiva and hard palatal mucosa were involved in 71.77% (394/549) of cases, with remaining cases involving the mandibular gingiva and the floor of mouth (12.39%), the labial mucosa/lips (6.19%), the buccal mucosa (4.92%), the