

Effect of EMLA Pre-treatment on Capsaicin-induced Burning and Hyperalgesia

GIL YOSIPOVITCH¹, HOWARD I. MAIBACH² and MICHAEL C. ROWBOTHAM³

¹Department of Dermatology, Rabin Medical Center, Campus Beilinson Petah Tiqva, Israel and ²Department of Dermatology, ³Neurology and Anesthesia University of California, San Francisco, USA

Capsaicin, which has been studied extensively as a treatment for itch and several chronic pain disorders, induces burning during the first week of therapy, causing a substantial percentage of patients to discontinue treatment prematurely. We examined whether pre-treatment with the topical anesthetic EMLA reduces the burning sensation induced by capsaicin and alters capsaicin effects on thermal sensation and pain thresholds. Healthy adult volunteers participated in the single-blind, 6-day study. After baseline measurement of warmth, cold pain and heat pain thresholds with a computerized thermal sensory analyzer, subjects applied EMLA thrice daily on one forearm and vehicle placebo on the other forearm, 60 min before applying capsaicin 0.075% on both forearms. Subjects rated burning sensations 3 times a day throughout the study. After 1 and 5 days of thrice daily application of EMLA or vehicle followed by capsaicin, thermal sensory testing was repeated. Subjects rated burning sensations to be significantly less on the EMLA pre-treated forearm compared with the placebo pre-treated forearm during all 5 days of treatment ($p < 0.01$). Capsaicin with and without EMLA produced significant heat pain hyperalgesia and cold pain hypoalgesia after 1 day of treatment. After 5 days of treatment, heat pain hyperalgesia persisted on both forearms; however, it was significantly less on the EMLA-treated forearm vs the vehicle-treated site ($p < 0.03$). Cold pain hypoalgesia persisted in both forearms. The warmth sensation threshold was significantly higher on the EMLA-pre-treated forearm after 1 and 5 days of treatment. In conclusion, pre-treatment with EMLA significantly reduced the burning sensation from capsaicin and attenuated heat hyperalgesia during treatment. **Key words:** thermal testing; heat hyperalgesia; thermal thresholds.

(Accepted September 7, 1998.)

Acta Derm Venereol (Stockh) 1999; 79: 118–121.

G. Yosipovitch, Department of Dermatology, Rabin Medical Center, Petah Tiqva 49100, Israel.

Capsaicin, derived from the pungent substance in hot chilli peppers, is used as a topical therapy for conditions involving pain, pruritus and inflammation. With chronic use the severity of pain in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis, and the severity of uremic pruritus have all been reported to be significantly reduced (1–4). A major problem encountered with application of capsaicin is that it causes sensations of burning and hyperalgesia in up to 80% of patients (1, 5). This effect causes patients to withdraw from treatment before deriving any benefit.

Pre-treatment with topical local anesthetic has been suggested as a mean of reducing capsaicin-induced burning (6), but has not been subjected to a blinded, prospective clinical trial. The current study was undertaken to determine whether

pre-treatment with EMLA (Eutectic Mixture of Local Anesthetics, Astra Pharmaceuticals), a mixture of 2.5% lidocaine and 2.5% prilocaine, would prevent capsaicin-induced burning and hyperalgesia over a 5-day period of 3 daily applications of 0.075% capsaicin cream.

MATERIALS AND METHODS

Subjects

Five men and 5 women, aged 33–54 years (9 white, 1 hispanic) entered the study. After 2 applications of capsaicin, 1 subject dropped out due to severe capsaicin-induced pain. This subject's data are not included in the analysis.

Protocol summary

Healthy adult volunteers were recruited for the 6-day, single-blind, 3-session study. All subjects gave informed consent prior to participation and the study was approved by the Committee on Human Research at the University of California, San Francisco (UCSF), USA. After baseline ratings and thermal sensory measurements were performed, drug application began the same evening. Subjects applied EMLA to the left volar forearm 60 min before applying capsaicin 0.075% on the same area. On the right volar forearm, subjects applied EMLA vehicle before capsaicin application. Subjects followed this routine 3 times a day on both forearms for the next 5 days. To ensure correct application of study compounds and to check for skin irritation or breakdown, subjects were examined on 4 of the 5 days after capsaicin application had begun.

Thermal sensory thresholds were measured prior to the first application of study compounds, after the third application of capsaicin (within 24 h of the first application) and after 5 days of capsaicin application.

Application of EMLA, EMLA vehicle and capsaicin

Three times a day (at 08.00 h, 13.00 h and 19.00 h) subjects applied approximately 1 ml EMLA (2.5% lidocaine and 2.5% prilocaine, Astra, Södertälje, Sweden) on the left volar forearm over a 30 cm² area marked with a surgical pen 60 min before applying a similar amount of capsaicin 0.075% (Ferndale Laboratories, Ferndale, Michigan, USA). One application cycle was directly observed by the authors on 4 of the 5 days of the study. On the right volar forearm, subjects applied a placebo vehicle containing polyxyethylene fatty acid esters over a 30 cm² area 60 min before applying a similar amount of capsaicin. By the end of the study, subjects had applied capsaicin 15 times to each forearm.

Measurements of thermal thresholds and painful burning sensations

Measurements of thresholds for warmth sensation, heat pain and cold pain were obtained in both forearms using a peltier thermode device (TSA 2001, Medoc, Ramat Yishai, Israel). The probe holding temperature was 32°C and the contact area was 12.5 cm². Using the method of limits (7) the threshold was determined as the average of 4 successive stimuli for warmth sensation and 3 for cold pain and heat pain. Probe temperature change rates of 1°C/s were used for warmth threshold and 2°C/s for heat pain and cold pain thresholds. A period of 5 s elapsed before switching to the next thermal sensory modality. Thermal sensory thresholds were measured prior to the first application of study

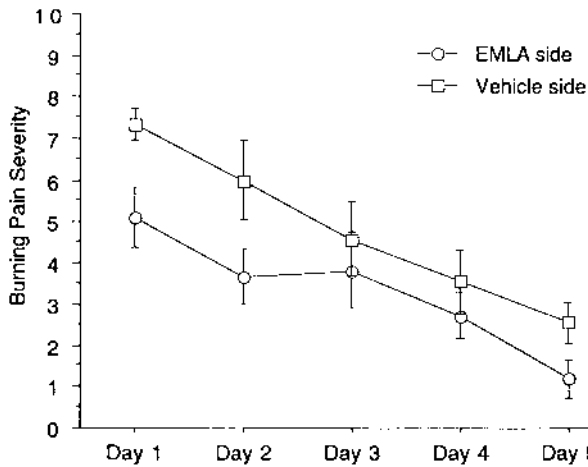


Fig. 1. Severity of burning pain on a 0–10 scale over 5 days of capsaicin application. Ratings are the average for each day of the 3 ratings made 1 h after each capsaicin application. Pre-treatment with EMLA 60 min before capsaicin application attenuated capsaicin induced burning on all 5 days with greatest effect in the first 2 days $p=0.01$.

compounds, 40–60 min after the third application of capsaicin and after 5 days of capsaicin application.

Each subject made written ratings of burning pain (Burn VAS) in the treated area of each forearm 3 times a day, using a 10 cm visual analog scale line marked in 1 cm increments between “no burning” and “worst burning possible”. Ratings were made 1 h after each capsaicin application.

Data analysis

Baseline thermal thresholds were compared within subjects for equivalence of the 2 forearms by two-tailed, paired t -test. Changes from baseline thermal thresholds after 3 and 15 applications of capsaicin were analysed by paired t -test for each arm separately. Likewise, the magnitude of the changes in the thermal thresholds in the EMLA-treated arm and the EMLA vehicle-treated arm were also compared by paired t -test.

The difference in Burn VAS between the EMLA-treated and EMLA-vehicle treated arms was compared for the average of the first 3 and the last 3 capsaicin applications using the Mann-Whitney U test. Changes in the Burn VAS for the 2 arms from the first 3 to the last 3 capsaicin applications were compared using Wilcoxon's signed rank test.

RESULTS

Burning pain

No subject reported burning with application of EMLA and EMLA vehicle prior to capsaicin. As shown in Fig. 1, over the 5 days of capsaicin application, burning pain was significantly less on the EMLA-pre-treated forearm than the vehicle-treated side. Four subjects reported an exacerbation of burning sensation when exposed to sun. Subjects found the cooling stimulus soothing for their spontaneous burning sensation.

Effects of capsaicin pre-treatment on cutaneous sensations after 1 day of treatment

Table I summarizes the changes in thermal thresholds measured after 1 day of treatment. Warmth sensation threshold was significantly elevated by capsaicin with EMLA (34.8°C vs 33.7°C baseline), as shown in Fig. 2. Capsaicin with vehicle

Table I. The effect of capsaicin with EMLA and with vehicle on warm sensation threshold (WS) heat (HP) and cold pain (CP) thresholds after 1 and 5 days' application

	1 day application		5 day application	
	Mean difference $^{\circ}\text{C}$	p value	Mean difference $^{\circ}\text{C}$	p value
WS baseline vs WS cap EMLA	-1.18	0.02	-1.06	0.01
WS baseline vs WS cap vehicle	0.06	0.70	0.08	0.5
WS cap EMLA vs WS cap vehicle	1.17	0.01	1.07	0.01
HP baseline vs HP cap EMLA	2.05	0.02	1.67	0.02
HP baseline vs HP cap placebo	4.50	0.01	4.55	0.01
HP cap EMLA vs HP cap vehicle	1.89	0.09	2.33	0.03
CP baseline vs CP cap EMLA	6.50	0.02	8.1	0.01
CP baseline vs CP cap vehicle	8.45	0.02	9.6	0.01
CP cap EMLA vs CP cap vehicle	-1.27	0.44	0.38	0.5

slightly reduced warmth thresholds. Capsaicin with and without EMLA caused significant hyperalgesia to heat pain. Heat pain thresholds were reduced by 2.05°C on the EMLA side and 4.5°C on the vehicle side (Fig. 3). Treatment with EMLA caused 1.9°C less heat pain hyperalgesia than pre-treatment with vehicle, but the asymmetry only approached statistical significance. Capsaicin caused significant hypoalgesia to cold thresholds on both the EMLA- and vehicle-treated sides by 6.5°C and 8.45°C , respectively, but without a significant difference between the sides. After capsaicin treatment started, subjects found the cooling stimulus soothing.

Effects of capsaicin pre-treatment on cutaneous sensation after 5 days of treatment

Table I summarizes the changes in thermal thresholds after 5 days of treatment. Warm sensation threshold continued to be significantly elevated compared with baseline on the capsaicin with EMLA-treated side (Fig. 2).

Compared with baseline heat pain hyperalgesia persisted on both sides. However, heat hyperalgesia was significantly less on the EMLA-treated side than the vehicle-treated side (39.8°C vs 37.4°C) as shown in Fig. 3.

Cold pain hypoalgesia intensified still further after 5 days of treatment on both sides, with no significant difference between the sides.

DISCUSSION

Up to 80% of patients report stinging and burning after application of capsaicin, particularly during the first week of therapy (1). This is believed to be due to the initial release of substance P from sensory neurons. Sensory irritation is the main cause of patient withdrawal from treatment. In clinical

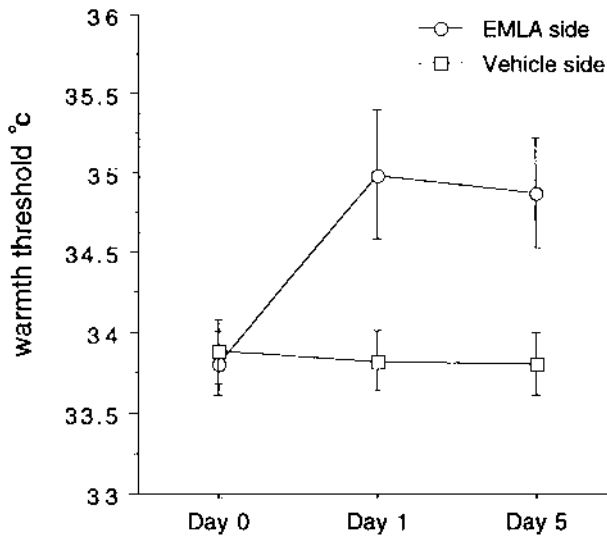


Fig. 2. Warmth thresholds at baseline without medications (day 0), at 60 min after the third capsaicin application (day 1) and at 60 min after the fifteenth capsaicin application (day 5). EMLA pre-treatment significantly elevated warmth thresholds compared with vehicle pre-treatment at both day 1 and day 5.

trials, withdrawal rates were up to 30% for patients with post-herpetic neuralgia (8). The present single-blind study demonstrates that pre-treatment with EMLA significantly reduced capsaicin-induced burning during the first 5 days of treatment and also heat pain hyperalgesia as shown by quantitative thermal testing. However, pre-treatment with EMLA did not eliminate totally the burning sensation produced by capsaicin but decreased its magnitude. It is of note that EMLA was applied without occlusion in a lower dose, than the usually recommended dosage for local anesthesia of the skin (about 2 g over an area of about 10 cm² with an occlusive dressing). Therefore, pre-treatment with EMLA during early weeks of topical capsaicin may increase the therapeutic usefulness of capsaicin.

Our results also show that the addition of EMLA has an effect on C fibers to elevate warm sensation threshold. Human psychophysical studies and animal studies show that capsaicin initially excites C-primary afferents, producing a spontaneous burning sensation, heat hyperalgesia and neurogenic vasodilatation (4, 9). After several weeks of multiple applications of 0.075% capsaicin daily, heat pain thresholds rise and neurogenic vasodilatation is reduced (10). The effect of EMLA in reducing burning sensation could be attributed to local anesthetic effects on cutaneous unmyelinated primary afferents, as reflected in the elevated threshold for warmth on the EMLA-treated side. Lidocaine, an important constituent of EMLA, binds to specific sites associated with voltage sensitive Na⁺ channels and prevents channel opening in response to depolarizing stimuli (11–12). Capsaicin effect upon cutaneous C-nociceptors differs from those of EMLA since capsaicin causes depressive effects on C-nociceptors by preventing opening of calcium channels (13). Wallengren & Håkanson demonstrated that capsaicin-evoked axon reflex flare can be abolished by pre-treatment with a local anesthetic (EMLA) and that the tachyphylaxis produced by repeated topical applications of capsaicin was not affected by repeated pre-treatment applications of EMLA (14). Our results after 5 days of treatment are in agreement with their study. Local anesthetic pre-treated rats with

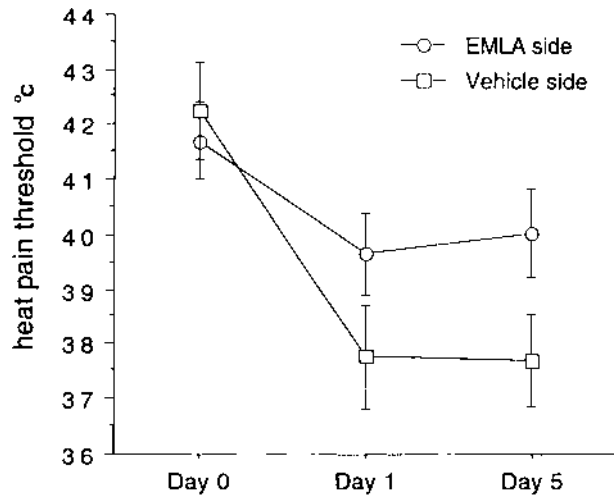


Fig. 3. Heat pain thresholds at baseline without medications (day 0), at 60 min after the third capsaicin application (day 1) and at 60 min after the fifteenth capsaicin application (day 5). Compared with vehicle, EMLA pre-treatment significantly attenuated capsaicin induced heat pain hyperalgesia at both day 1 and day 5.

the capsaicin-like compound RTX showed decreases in licking behavior from the first to subsequent applications of RTX suggesting that local anesthetic can attenuate the irritancy of initial treatment with RTX without disrupting development of desensitization of sensory afferents (15). These results and our findings suggest that the neuropeptide depleting action of capsaicin on C-fibers is independent of the effect of EMLA on impulse flow in the C-fibers.

In the present study, capsaicin with and without EMLA caused heat pain hyperalgesia and cold pain hypoalgesia. Simone & Ochoa (10) investigated the effect of 8 weeks' topical treatment with capsaicin 0.075% in normal subjects. Heat-induced pain thresholds were initially decreased after 1 day of treatment, similar to our results, and became elevated after 6 weeks. However, capsaicin did not change cold pain thresholds in comparison with vehicle during this period. Our study shows a clear change in the mean thresholds for cold pain sensation, which remained significantly lower than pre-treatment values. Winter et al. (13) reported that topical capsaicin does not appear to change the thresholds of touch and cold. However Walker & Lewis (16) have shown that cold sensation was less intense with application of capsaicin. Bjerring & Arndt-Nielsen (17) found in humans that capsaicin has inhibitory effect on A delta fiber, mediated pricking pain, which gives logical support to our findings.

In conclusion, pre-treatment with EMLA before capsaicin application reduces the burning sensation from capsaicin and therefore might improve patient acceptance of capsaicin therapy during the first week. EMLA pre-treatment elevates warmth thresholds and attenuates capsaicin induced heat hyperalgesia. All observed effects of EMLA are consistent with its local anaesthetic effects on receptors and nociceptors.

REFERENCES

1. Rains C, Bryson HM. Topical capsaicin: a review of its pharmacological properties and therapeutic potential in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis. *Drug Aging* 1995; 7: 317–328.

2. Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin – a multicenter, double-blind, vehicle-controlled study. *Arch Intern Med* 1991; 151: 2225–2229.
3. Breneman DL, Cardone S, Blumsack RF, Lather RM, Searle EA, Pollack VE. Topical capsaicin for treatment of hemodialysis related pruritus. *J Am Acad Dermatol* 1992; 26: 91–94.
4. Lynn B. Capsaicin actions on C fibre afferents that may be involved in itch. *Skin Pharmacol* 1992; 5: 9–13.
5. Bernstein J. Capsaicin in dermatologic disease. *Semin Dermatol* 1988; 7: 304–309.
6. Watson CPN, Evans RJ, Watt VR. Post herpetic neuralgia and topical capsaicin. *Pain* 1988; 33: 333–340.
7. Yosipovitch G, Yarnitsky D. Quantitative sensory testing, In: Marzulli FN, Maibach HI, eds, *Dermatotoxicology methods*. Taylor & Francis, Bristol, PA 1998: 313–317.
8. Rumsfield JA, West D. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP Ann Pharmacother* 1991; 25: 381–387.
9. Carpenter SE, Lynn B. Vascular and sensory responses of human skin to mild injury after topical treatment with capsaicin. *Br J Pharmacol* 1981; 73: 755–758.
10. Simone DA, Ochoa J. Early and late effects of prolonged topical capsaicin on cutaneous sensibility and neurogenic vasodilatation in humans. *Pain* 1991; 47: 285–294.
11. Catterall WA. Common modes of drug action on Na⁺ channels: local anaesthetics, antiarrhythmics and anticonvulsants. *Trends Pharmacol Sci* 1987; 8: 57–65.
12. Devor M, Wall P, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 1992; 48: 261–268.
13. Winter J, Bevan S, Campbell EA. Capsaicin and pain mechanisms. *Br J Anaesth* 1995; 75: 157–168.
14. Wallengren J, Håkanson R. Effects of capsaicin, bradykinin and prostaglandin E2 in the human skin. *Br J Dermatol* 1992; 126: 111–117.
15. Craft RM, Porreca F. Tetracaine attenuates irritancy without attenuating desensitization produced by intravesical resiniferatoxin in the rat. *Pain* 1994; 57: 351–359.
16. Walker F, Lewis S. Somesthetic and electrophysiologic effects of topical 0.025% capsaicin in man. *Reg Anesth* 1990; 15: 61–66.
17. Bjerring P, Arendt-Nielsen L. A quantitative comparison of the effect of local analgesics on argon laser induced cutaneous pain and on histamine induced wheal, flare and itch. *Acta Derm Venereol (Stockh)* 1990; 70: 126–131.