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Safety and Efficacy of Vocacapsaicin for Management of Postsurgical Pain: A Randomized Clinical Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- No locally administered analgesic provides relief for more than 48 h after surgery
- Capsaicin produces sustained analgesia without loss of sensation, proprioception, or muscle strength by activating transient receptor potential vanilloid subfamily member 1 receptors on C-fiber nociceptors, the nerves that mediate dull, aching pain after surgery
- Vocacapsaicin, a novel water-soluble prodrug, rapidly releases capsaicin at the surgical site after local administration during surgery

What This Article Tells Us That Is New

- A triple-blinded, randomized, placebo-controlled trial compared three doses of intraoperative locally administered vocacapsaicin to placebo in 147 patients undergoing bunionectomy, a standard model of postsurgical pain
- In patients receiving 14 ml of vocacapsaicin (0.30 mg/ml), the median (95% CI) decrease in pain at rest over the first 96 h was 33% (10 to 52%) despite a 50% (26 to 67%) decrease in opioid consumption compared to patients receiving placebo and otherwise identical perioperative anesthesia and postoperative analgesia
- There was no difference in the rate, type, or severity of adverse events among the four study groups

ABSTRACT

Background: Nonopioid management of postsurgical pain remains a major unmet need. Few studies have evaluated transient receptor potential vanilloid subfamily member 1 agonists for analgesia after surgery. This study examines intraoperative vocacapsaicin, a novel prodrug of the transient receptor potential vanilloid subfamily member 1 agonist capsaicin, in a validated model of postsurgical pain.

Methods: This was a triple-blinded, randomized, placebo-controlled, dose-ranging trial in patients undergoing bunionectomy. Patients were randomized 1:1:1:1 to surgical site administration of 14 ml of placebo or one of three vocacapsaicin concentrations: 0.30, 0.15, or 0.05 mg/ml. The prespecified primary endpoint was the area-under-the-curve of the numerical rating scale pain score at rest through 96 h for the 0.30 mg/ml group. Prespecified ordered, secondary endpoints for the 0.30 mg/ml group included the percentage of patients who did not require opioids from 0 to 96 h, total opioid consumption through 96 h, and the area-under-the-curve of the numerical rating scale pain score for the first week.

Results: The 147 patients were randomized. During the first 96 h, vocacapsaicin (0.30 mg/ml) reduced pain at rest by 33% *versus* placebo (primary endpoint, 95% CI [10%, 52%], effect size [Cohen's d] = 0.61, $P = 0.005$). Of patients receiving vocacapsaicin (0.30 mg/ml), 26% did not require postoperative opioids for analgesia ($P = 0.025$) *versus* 5% of patients receiving placebo. Vocacapsaicin (0.30 mg/ml) reduced opioid consumption over the first 96 h by 50% *versus* placebo (95% CI [26%, 67%], effect size = 0.76, $P = 0.002$). Vocacapsaicin (0.30 mg/ml) reduced pain over the first week by 37% *versus* placebo (95% CI [12%, 57%], effect size = 0.62, $P = 0.004$). The treatment effect persisted for at least 2 weeks. All study endpoints showed an administered concentration-*versus*-response relationship. Vocacapsaicin was well tolerated with no differences between groups in any safety parameter.

Conclusions: A single, local administration of vocacapsaicin during surgery reduced pain and opioid consumption for at least 96 h after surgery compared to control.

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Effective management of pain after surgery is an unmet medical need.[1–5] Oral opioid analgesics remain an integral part of postsurgical pain management[1,2] despite common side effects, safety concerns, and the risk of persistent

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opioid use.[6–8] Acute side effects can interfere with recovery, whereas persistent opioid use has risks to both the patient and overall public health.[9–11]

Treating postsurgical pain at its source, the nociceptor, is considered an ideal approach.[12–15] To date, no locally administered analgesic provides relief for more than 48 h after surgery.[16–23]

Capsaicin is a highly selective agonist of the transient receptor potential vanilloid subfamily member 1 (TRPV1) ion channel, which is expressed on unmyelinated (C-fiber) nociceptors. TRPV1 is unique among drug targets in that its initial excitation caused by brief exposure to agonists is followed by a long-lasting refractory state (traditionally referred to as desensitization).[24] Exposure to a single, therapeutic dose of capsaicin results in a durable (up to months) but fully reversible state in which the previously excited neurons remain unresponsive to stimuli, providing durable analgesia.[24] The prolonged analgesia after a single dose of capsaicin is a result of C-fiber desensitization and does not require the continued presence of capsaicin.

A topical 8% capsaicin patch approved by the Food and Drug Administration provides up to 3 months of pain relief after a single application in patients with neuropathic pain.[25] Capsaicin administration has also been studied in the treatment of pain associated with osteoarthritis[26] (intra-articular injection), Morton's neuroma[27] (small volume injection directly into the neuroma), and postsurgical pain[14] (instillation of a viscous solution into the surgical site followed by removal with suction after 5 min).

Vocacapsaicin, a novel, water-soluble prodrug, designed specifically for tissue infiltration, rapidly releases capsaicin at the surgical site after local administration.[28] With a water solubility of greater than 50 mg/ml, vocacapsaicin is greater than 100-fold more soluble than capsaicin, allowing for delivery in standard, aqueous pharmaceutical solutions. At physiologic pH, vocacapsaicin rapidly releases capsaicin *via* a pH-dependent, intramolecular cyclization reaction, resulting in a half-life of less than 5 min. After administration, the surgical site is rapidly exposed to therapeutic levels of capsaicin. Systemic prodrug levels are low and transient. Capsaicin and the resultant cyclic urea reach maximum plasma levels within 1 to 2 h after administration and have a short duration of systemic exposure.

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This triple-blinded, randomized, placebo-controlled trial compared intraoperative local administration of vocacapsaicin to placebo in patients undergoing bunionectomy, a well recognized and predictive postsurgical pain model.[29–31] Other than administration of the study medication, all patients received identical perioperative analgesia including a local anesthetic block, acetaminophen, and ketorolac. Efficacy endpoints included pain relief and opioid use.

Materials and Methods

After institutional review board approval and with written informed consent, we conducted a phase 2, multicenter, randomized, triple-blinded, placebo-controlled study of vocacapsaicin in patients undergoing osteotomy with realignment and internal fixation (bunionectomy; registry information: ClinicalTrials.gov NCT03599089; date of registration, July 17, 2018; principal investigator, Jon L. Ruckle, M.D., C.P.I.). Other than the study drug, all patients received identical perioperative analgesia. The patients were randomized 1:1:1:1 in parallel groups to 14 ml of either 0.05 mg/ml vocacapsaicin (0.7 mg), 0.15 mg/ml vocacapsaicin (2.1 mg), 0.30 mg/ml vocacapsaicin (4.2 mg), or vehicle (normal saline with mannitol and citrate buffer). The doses were selected based on results from a pilot phase 1 study that evaluated doses in the same range (currently unpublished; results available at ClinicalTrials.gov NCT03307837).

Operative Procedure and Postoperative Analgesia

All patients underwent a standard bunionectomy with light to moderate sedation. All patients received 30 mg of ketorolac, 1 g of acetaminophen, and a field block that anesthetized the specific nerves of the forefoot ("Mayo block") with 20 to 30 ml of 0.5% bupivacaine HCl that was placed at least 3 cm proximal to the surgical site.[32] Before wound closure, the surgeon administered 14 ml of the blinded study drug solution by infiltration (injection through a needle) and instillation (administration onto the wound) into the soft tissues and osteotomy surgical sites as follows: 2 ml instilled onto osteotomy surfaces, 9 ml infiltrated circumferentially into the deep soft tissue, 2 ml into the closed capsule space, and 1 ml instilled onto the exposed wound surface before closure. The surgeons and all assessors were blinded as to study drug allocation.

Patients were observed for 96 h in a research facility to allow standardized collection of study data. During the first 96 h, as per this standardized, experimental postsurgical pain model,[31] no analgesics other than opioids were given. Rescue opioid analgesia with 5 mg of oxycodone could be requested at any time for inadequately controlled pain. Subjects were encouraged to request rescue medication only when experiencing moderate-to-severe pain with a numeric rating scale (NRS) pain score greater than or equal to 4. Numeric rating pain scores were completed within 15 min before rescue medication to document the

pain leading to rescue medication request. After discharge, patients were prescribed multimodal analgesia with ibuprofen and/or acetaminophen as needed for mild-to-moderate pain and opioid analgesics for moderate-to-severe breakthrough pain. Further details are contained in the study protocol available in the supplemental digital content (https://links.lww.com/ALN/D546).

Data Collection

Time 0 was completion of study drug administration. Day 0 was the day of surgery. The subjects were monitored for 96 h after surgery at the study site and discharged on day 4. Serial safety and efficacy evaluations, including recording of adverse events, were performed at prespecified times. Subjects returned to the study center on days 8, 15, and 29 for additional follow-up. Subjects discontinued from the study were last evaluated at the time of discontinuation.

Pain at rest and after walking (evoked pain) were measured using a standard 11-point, 0 to 10 NRS, where 0 is no pain, and 10 is the worst imaginable pain. NRS pain score at rest was documented every 4 h (while awake) during the first 96 h and twice daily after discharge through 2 weeks. Evoked NRS pain score was documented twice daily through 2 weeks. In addition, the NRS pain score triggering the use of any opioids ("triggering NRS pain score") was always recorded before opioid rescue. Opioid consumption (OC) was measured after converting oxycodone dose into oral morphine equivalents (OME; 1 mg of oxycodone = 1.5 mg OME).[33] After discharge, the subjects recorded in a diary NRS pain scores twice daily, as well as the time and dose of all analgesic medications.

Serial safety assessments included adverse events, vital signs, wound healing, clinical laboratory testing, and quantitative neurosensory testing. Further details on adverse event collection, classification, and reporting are described in the study protocol available in the supplemental digital content (https://links.lww.com/ALN/D546).

Statistical Analysis

The primary efficacy variable was the area under the curve (AUC) of the NRS pain scores at rest from 0 to 96 h ($AUC_{0–96h}$) calculated as the trapezoidal area under the NRS pain score data points between observations (NRS × h). Cumulative pain over time (NRS pain score AUC) is the endpoint required for regulatory approval, and the interval was selected prospectively based on the results of previous studies of capsaicin instillation for postsurgical pain.[12]

Because opioids decrease subsequent pain scores, any scheduled NRS pain score at rest that occurred within a 4-h window after an oxycodone dose was imputed using the previous "triggering" NRS pain score ("windowed last observation carried forward" method).[34] NRS pain score with ambulation were not censored after opioid administration because obtaining a previous NRS with ambulation would require asking a patient to ambulate before receiving the opioid. Missing scheduled NRS pain scores for patients who discontinued the study before the last study observation were imputed from the worst NRS pain score recorded for the subject (*i.e.*, "worst observation carried forward").

The sample size of the current study was based on a pilot phase 1 study (currently unpublished, results available at ClinicalTrials.gov NCT03307837) in which the mean difference in $AUC_{0–96h}$ at rest between the three vocacapsaicin groups and the placebo group was −120 NRS × h, with a median SD of 108. The current study was powered to detect a difference in the primary endpoint between vocacapsaicin (0.30 mg/ml) *versus* placebo administration in patients receiving identical analgesic regimens. Assuming the true difference to be −100 NRS × h, a SD of 130 NRS × h, a study with 90% power, and $\alpha = 0.05$ required 36 subjects in each group. This determined the overall study size of 36 subjects in each of four groups.

The primary endpoint was the difference in the pain at rest $AUC_{0–96h}$ between patients receiving vocacapsaicin (0.30 mg/ml) and patients receiving placebo. The prespecified, α-conserving, sequential hierarchy of secondary endpoints in the vocacapsaicin (0.30 mg/ml) group were the percentage of subjects who did not require opioids ("opioid-free") from 0 to 96 h ($OF_{0–96h}$), total OC in OME from 0 to 96 h ($OC_{0–96h}$), and the difference in the pain at rest AUC for the first week ($AUC_{0–168h}$).

Unless otherwise specified, statistical significance for AUC was analyzed using a one-factor (treatment) ANOVA model with treatment as the main effect. Statistical significance for the proportion of patients that were opioid-free was calculated using a logistic regression.

Primary and secondary comparisons between the placebo and vocacapsaicin (0.30 mg/ml) groups were made using a two-sided test at the $\alpha = 0.05$ level of significance. The type I overall error rate was maintained at $\alpha = 0.05$ through multiple comparisons using sequential, hierarchical testing in the order presented above. Once $P \geq 0.05$ was found, subsequent endpoints in the secondary hierarchy were considered exploratory rather than confirmatory.

Prespecified exploratory endpoints included differences in pain at 48, 96, 168, and 336 h; pain at rest AUC for 2 weeks ($AUC_{0–336h}$); total OC for the first 2 weeks ($OC_{0–336h}$); pain at rest AUC after the inpatient observation period through 2 weeks ($AUC_{96–336h}$); total OC after the inpatient observation period through 2 weeks ($OC_{96–336h}$); and evoked pain AUC 0 to 168 h and 0 to 336 h ($AUC_{0–168h}$ with ambulation and $AUC_{0–336h}$ with ambulation, respectively). The *P* values for exploratory endpoints were descriptive and reported without adjustment for multiplicity. Administered concentration–*versus*–response relationships were assessed with a linear trend test.

Persistence of analgesic response was documented by visually comparing to placebo the NRS pain scores for

vocacapsaicin groups during the 2 weeks after surgery. NRS pain score AUC is reported in units of NRS × h, which is difficult to interpret. We calculated the percentage of reduction in AUC, a more clinically interpretable result, as the median and 95% confidence bounds from 10,000 bootstrap replications of the data.

Opioid cessation was described with Kaplan–Meier survival analysis of opioid use over the 2-week observation period. The censoring window for patients still taking opioids at the end of the 2 weeks was determined by analysis of the time gaps in opioid use while patients were still consuming opioids. The CI values for the Kaplan–Meier analysis were determined with bootstrap resampling with 100,000 repetitions.

All analyses were performed on the modified intent-to-treat population (all patients that received any study drug), which was the same as the intent-to-treat population (all randomized patients; see fig. 1). All analyses were performed in SAS version 9 (SAS Institute, USA) except for the bootstrap and Kaplan–Meier analyses, which were performed in R 4.3.2 "Eye Holes", (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 147 subjects were randomized at three sites, as shown in table 1. There were no meaningful differences in the study population demographics among the four groups.

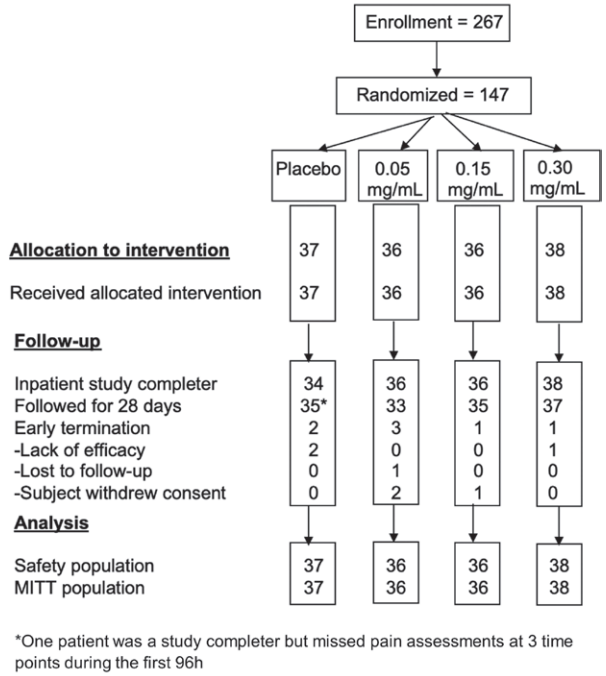

Fig. 1. Consort diagram. *Refused further study procedures but did not withdraw consent to include their data. MITT, modified intent to treat.

All patients were included in both the efficacy and safety analyses.

Patient flow appears in figure 1. Two subjects in the placebo group dropped out before 96 h due to inadequate analgesia. No subjects in the vocacapsaicin groups terminated during the inpatient portion of the study. No subjects were excluded from the data analysis.

Primary and Secondary Endpoints

Figure 2 shows data for the primary and secondary study endpoints for all doses. For the primary endpoint, vocacapsaicin (0.30 mg/ml) reduced pain at rest over the first 4 days ($AUC_{0–96h}$) by 134 NRS × h ($P = 0.005$; median decrease, 33%; 95% CI [10%, 52%]; standardized effect size [Cohen's d], 0.61) when compared to patients receiving placebo (fig. 2A). $AUC_{0–96h}$ was reduced by 21% in the 0.05 mg/ml group ($P = 0.081$) and 20% in the 0.15 mg/ml group ($P = 0.099$), demonstrating an administered concentration-*versus*-response relationship ($P = 0.013$).

Vocacapsaicin demonstrated a statistically significant benefit in all secondary endpoints. Of patients administered vocacapsaicin (0.30 mg/ml), 26% did not require opioids through 96 h nor during the entire observation period, whereas only 5% of patients receiving placebo did not require opioids ($P = 0.025$), an absolute difference of 21% (fig. 2B). In addition, 19% of patients in the 0.05 mg/ml group and 17% of patients in the 0.15 mg/ml group and did not require any opioids ($P = 0.086$ and $P = 0.142$, respectively).

Over the first 4 days after surgery, vocacapsaicin (0.30 mg/ml) reduced OC by 28 OME ($P = 0.002$; median decrease, 50%; 95% CI [26%, 67%]; standardized effect size, 0.76; fig. 2C). Opioid consumption over the first 4 days was reduced compared to placebo by 24% in 0.05 mg/ml group ($P = 0.131$) and by 33% in the 0.15 mg/ml group ($P = 0.042$), demonstrating an administered concentration-*versus*-response relationship ($P = 0.003$).

Over the first week after surgery, vocacapsaicin (0.30 mg/ml) reduced pain at rest ($AUC_{0–168h}$) by 225 NRS × h compared to placebo ($P = 0.004$; median decrease, 37%; 95% CI [12%, 57%]; standardized effect size, 0.62; fig. 2D). $AUC_{0–168h}$ was reduced by 21% ($P = 0.109$) in the 0.05 mg/ml group and by 21% in the 0.15 mg/ml group ($P = 0.113$), demonstrating an administered concentration-*versus*-response relationship ($P = 0.009$).

Exploratory Endpoints

The exploratory endpoints are graphically shown in the supplemental digital content (supplement 2, https://links.lww.com/ALN/D547). Vocacapsaicin (0.30 mg/ml) reduced pain at rest at more than 2 weeks after surgery ($AUC_{0–336h}$) by 376 NRS × h ($P = 0.011$; median decrease

Table 1. Baseline Characteristics

Characteristic	0.05 mg/ml (N = 36)	0.15 mg/ml (N = 36)	0.30 mg/ml (N = 38)	Placebo (N = 37)	Total (N = 147)
Mean age (SD), yr	48.9 (12.3)	44.6 (12.3)	41.4 (12.2)	50.7 (12.5)	46.4 (12.7)
Female sex, N (%)	33 (92)	25 (69)	34 (90)	31 (84)	123 (84)
Race, N (%)					
White (non-Hispanic)	12 (33)	9 (25)	11 (29)	10 (27)	42 (29)
White (Hispanic)	8 (22)	11 (31)	8 (21)	12 (32)	39 (27)
Black	12 (33)	12 (33)	14 (37)	14 (38)	52 (35)
Other	4 (11)	4 (11)	5 (13)	1 (3)	14 (10)
ASA Physical Status, N (%)					
I	21 (58)	25 (69)	22 (58)	22 (60)	90 (61)
II	15 (42)	11 (31)	15 (40)	15 (41)	56 (38)
III	0.0	0.0	1 (2)	0.0	1 (1)
Weight, kg					
Mean (SD)	76.4 (16.5)	82.9 (19.1)	78.6 (13.8)	77.2 (15.1)	78.8 (16.2)
Median	71.9	82.3	78.7	78.9	78.0
Body mass index, kg/m^2					
Mean (SD)	28.4 (5.6)	28.8 (5.0)	28.3 (4.8)	28.3 (5.1)	28.5 (5.1)
Median	27.3	27.9	28.6	27.6	27.6
Nonsteroidal anti-inflammatory drugs, N (%)	4 (11)	3 (8)	6 (16)	3 (8)	16 (11)

No subjects were taking opioids.
ASA, American Society of Anesthesiologists.

compared to placebo, 37%; 95% CI [8%, 57%]; supplement 2, fig. A, https://links.lww.com/ALN/D547). Vocacapsaicin (0.30 mg/ml) reduced OC over the first 2 weeks by 36 OME (P = 0.001; median, 55%; 95% CI [30%, 72%]; supplement 2, fig. B, https://links.lww.com/ALN/D547).

After patients started receiving multimodal analgesia on day 4, vocacapsaicin (0.30 mg/ml) reduced pain at rest from day 4 through 2 weeks ($AUC_{96–336h}$) by 242 NRS × h (P = 0.028; median decrease, 40%; 95% CI [4%, 62%]; supplement 2, fig. C, https://links.lww.com/ALN/D547). Vocacapsaicin (0.30 mg/ml) reduced total OC from day 4 through 2 weeks by 8 OME (P = 0.035; median decrease compared to placebo, 90%; 95% CI [29%, 100%]; supplement 2, fig. D, https://links.lww.com/ALN/D547). Vocacapsaicin (0.30 mg/ml) reduced NRS pain score AUC with ambulation over the first week compared to placebo by 206 NRS × h (P = 0.012; median decrease, 30%; 95% CI [8%, 47%]; supplement 2, fig. E, https://links.lww.com/ALN/D547) and greater than 2 weeks by 334 NRS × h (P = 0.028; median decrease 30%; 95% CI [2%, 50%]; supplement 2, fig. F, https://links.lww.com/ALN/D547).

Pain over Time at Rest and with Ambulation

Figure 3 shows the mean NRS pain scores at rest and with ambulation over 2 weeks for patients receiving placebo and patients receiving vocacapsaicin (0.30 mg/ml). As expected, increased pain was reported in the vocacapsaicin groups in the first few hours after surgery. This is due to the initial excitation of TRPV1-expressing nociceptors by capsaicin.

The mean ± SD NRS pain score reported at 48 h was 4.6 ± 2.9 for the placebo group *versus* 2.8 ± 2.7 for the 0.30 mg/ml group, a 39% reduction (P = 0.005). The mean (SD) NRS pain score reported at 96 h was 3.0 ± 3.2 for the placebo group *versus* 1.5 ± 2.4 for the 0.30 mg/ml group, a 50% reduction (P = 0.010). The mean ± SD NRS pain score reported at 168 h was 2.3 ± 2.6 for the placebo group and 1.2 ± 1.8 for the 0.30 mg/ml group, a 49% reduction (P = 0.034). The mean ± SD NRS pain score reported at 336 h was 1.4 ± 2.0 for the placebo group and 1.1 ± 1.6 for the 0.30 mg/ml, a 21% reduction (P = 0.468). As shown in figure 3, continued analgesic response is evident in the NRS pain scores during the second week, even though the difference in NRS pain scores may not be clinically consequential after the first week.

Opioid Cessation

Analysis showed that patients who did not consume opioids for 48 h had reliably ceased OC for the remainder of the study. We therefore defined "opioid cessation" as the last dose before an interval of 48 h of observation without further opioid use. Patients that were opioid-free for the 0- to 96-h period continued to be opioid-free for the entire observation period. Our Kaplan–Meier analysis imposed a 48-h censoring window at the end of the study (*i.e.*, days 13 and 14). Any opioid taken in the last 48 h of observation might or might not constitute the last dose of opioid.

Figure 4 shows the Kaplan–Meier survival analysis for continued OC. The hazard ratio for continued opioid use in patients receiving vocacapsaicin (0.30 mg/ml) *versus* placebo was 0.56 (95% CI [0.39, 0.89]; P = 0.009; log-rank

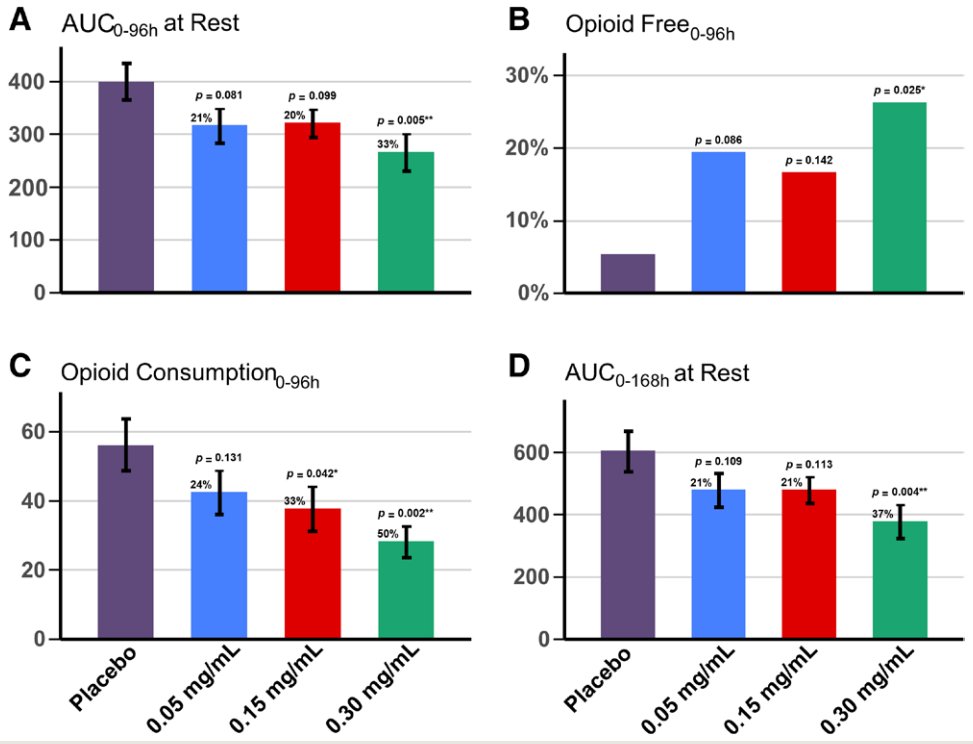

Fig. 2. Primary and secondary efficacy endpoints. Patients receiving vocacapsaicin (0.30 mg/ml) had less pain at rest over the first 96 h (AUC_{0-96h}; *A*, $P = 0.005$), were less likely to require any opioid (*B*, $P = 0.025$), consumed less opioid over the 4 days (*C*, $P = 0.002$), and had less pain at rest over the first week (AUC_{0-168h}; *D*, $P = 0.004$). The percentages in *panels A*, *C*, and *D* are the percentage reductions compared to placebo. All four endpoints were statistically significant. AUC, area under the numerical rating scale pain score at rest curve. *, $P < 0.05$; **, $P < 0.005$.

test). In other words, patients receiving placebo were generally twice as likely to be on opioids as patients receiving vocacapsaicin (0.30 mg/ml).

As shown in figure 4, patients receiving vocacapsaicin (0.30 mg/ml) had a median time to opioid cessation 23 h earlier than patients receiving placebo (95% CI [−4 h, 52 h]; $P = 0.074$). No patient receiving vocacapsaicin (0.30 mg/ml) required opioids after 5 days. Of patients in the placebo group, 16% continued to use opioids after 5 days while prescribed multimodal analgesia (95% CI [5 to 30%]; $P = 0.001$), 14% continued using opioids after 1 week (95% CI [3%, 24%]; $P = 0.005$), and 8% continued using opioids after 2 weeks (95% CI [0%, 19%]; $P = 0.044$).

Safety

Table 2 summarizes the adverse events observed by group during the study. There was no difference in the rate, type, or severity of adverse events among the four study groups. The observed adverse events are consistent with typical recovery from bunionectomy. This was true for both local and systemic effects. One subject in the placebo group experienced a serious adverse event of delayed cellulitis. There were no differences between groups in any other safety parameter.

Discussion

In this study of patients undergoing bunionectomy, a standard model of postsurgical pain, the addition of vocacapsaicin (0.30 mg/ml) produced a notable, long-lasting treatment effect on pain and opioid use with clinically and statistically significant reductions in the primary and all key secondary efficacy endpoints compared to patients receiving identical analgesia except for perioperative vocacapsaicin. Reduced analgesic efficacy was seen with lower concentrations of vocacapsaicin, demonstrating a dose–response relationship.

Despite withholding multimodal analgesia during the first 4 days as part of the experimental pain model, 36 of 38 patients in the vocacapsaicin (0.30 mg/ml) group ceased taking opioids within 4 days. The remaining two patients in vocacapsaicin (0.30 mg/ml) group ceased taking opioids the following day. Three patients (8%) in the placebo group still required opioid analgesia after 14 days, despite access to multimodal analgesia after 4 days. The risk of persistent postoperative opioid use increases most sharply in the initial days of therapy, particularly after 5 days.[35] Reducing the number

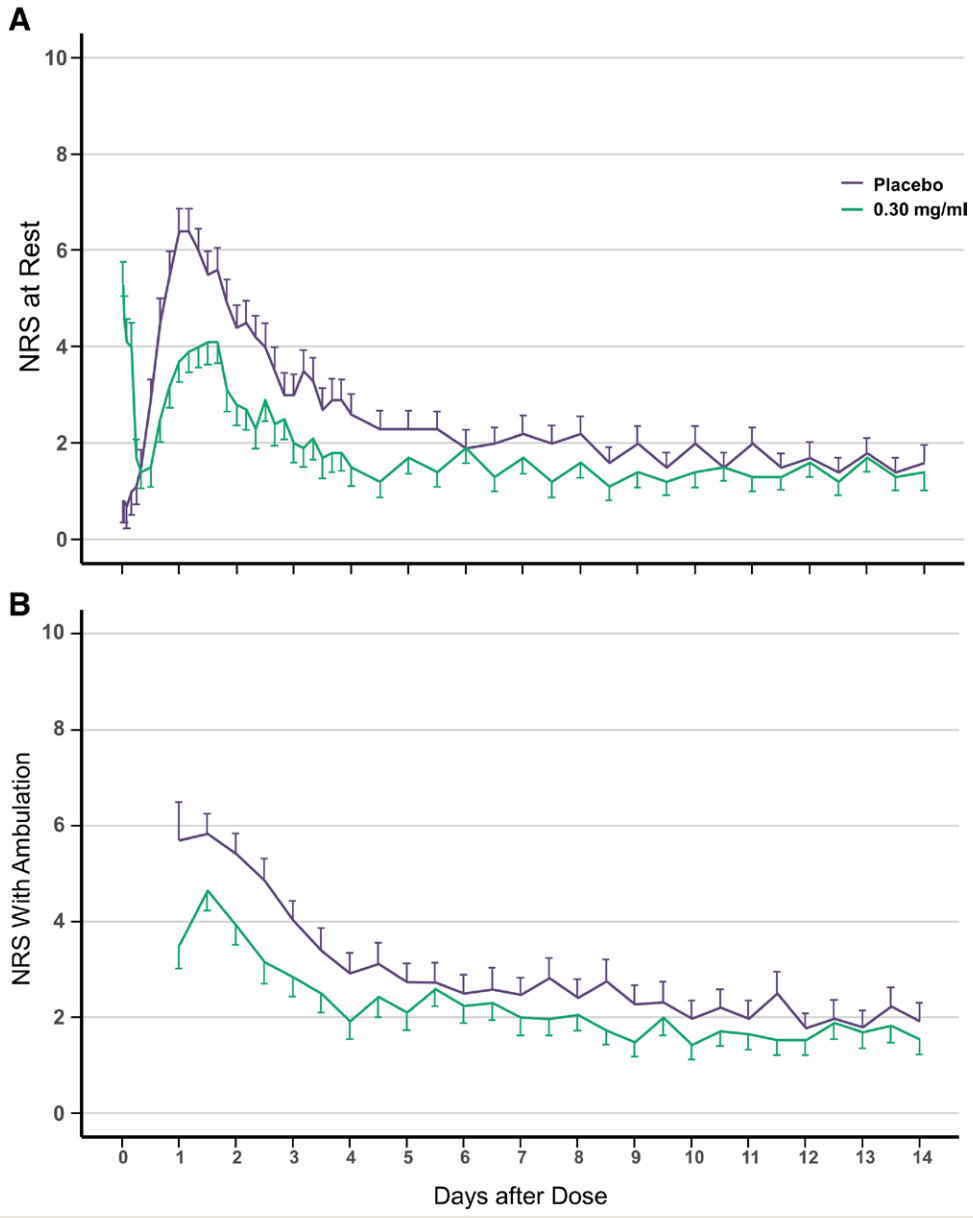

Fig. 3. Numerical rating scale (NRS) pain score at rest (*A*) and with ambulation (*B*) demonstrated sustained analgesic response in patients treated with 0.30 mg/ml vocacapsaicin compared to patients receiving placebo (mean ± standard error).

of patients requiring postoperative opioids and earlier cessation of opioid use are both clinically meaningful metrics.[36,37]

Our effect size of 0.61 is a moderate to strong effect.[38] Daniels *et al.*[39] compared postoperative acetaminophen, ibuprofen, and the combination of acetaminophen and ibuprofen to placebo after bunionectomy surgery. We can calculate effect sizes from the published data. Ibuprofen has an analgesic effect size of 0.49 *versus* placebo. Acetaminophen has an effect size of 0.53 *versus* placebo. The fixed dose combination of ibuprofen and acetaminophen has an effect size of 1.1 *versus* placebo. The standardized effect size of vocacapsaicin is higher than the standardized effect size of either ibuprofen or acetaminophen when given as sole postoperative analgesics for bunionectomy. When acetaminophen and ibuprofen are combined, the combination of drugs with different mechanisms of action leads to analgesic synergy (standardized effect size = 1.1), confirming the importance of combining drugs with different mechanisms of action.

A recent study reviewed the analgesic potency of VX-548 in a bunionectomy and abdominoplasty model.[5] The effect size (Cohen's d) for the highest dose was 0.41 for bunionectomy an 0.42 for abdominoplasty. These data suggest that the effect size for vocacapsaicin (0.30 mg/ml) in

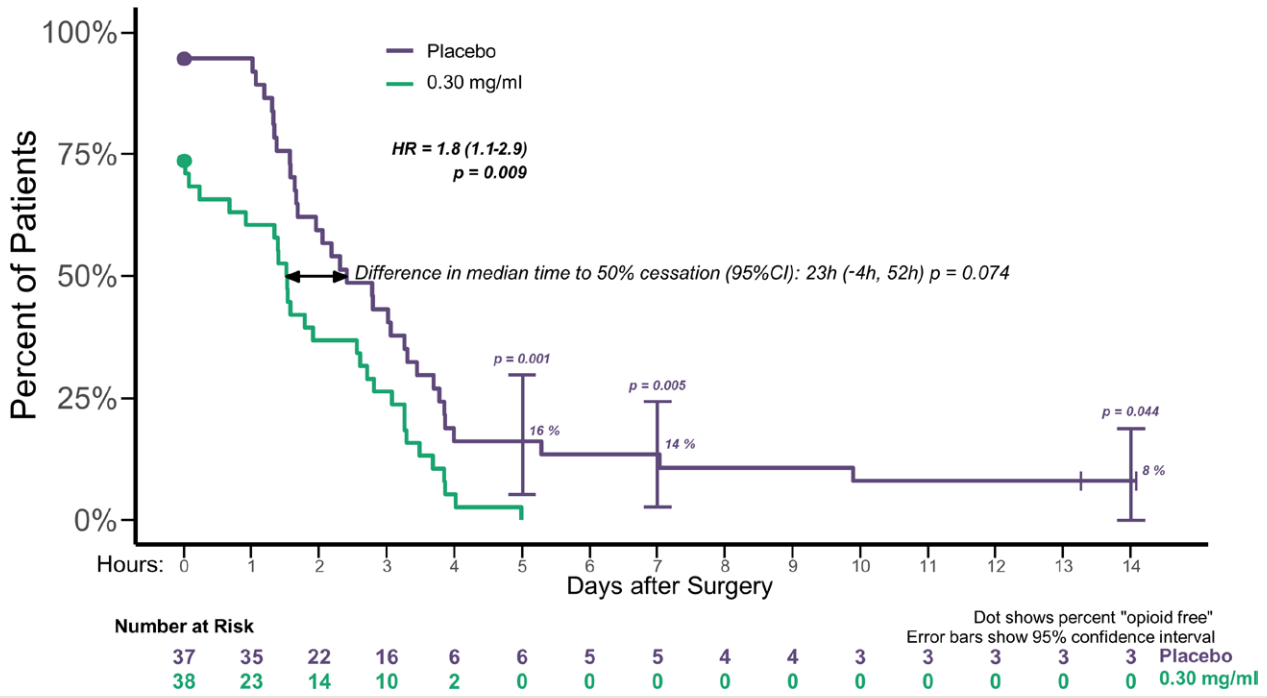

Fig. 4. Survival analysis showing the rate of opioid cessation in patients receiving placebo or vocacapsaicin (0.30 mg/ml). HR, hazard ratio.

Table 2. Summary of TEAEs

TEAE	0.05 mg/ml (N = 36)	0.15 mg/ml (N = 36)	0.30 mg/ml (N = 38)	Placebo (N = 37)	Total (N = 147)
Event, N (%)					
Any TEAE	27 (75)	28 (78)	26 (68)	25 (68)	106 (72)
Any severe TEAE	2 (5.6)	2 (5.6)	2 (5.3)	0	6 (4.1)
TEAE leading to discontinuation	0	0	0	0	0
Any serious adverse event	0	0	0	1 (2.7)	1 (0.7)
Nervous system disorders					
Burning sensation	2 (5.6%)	0	2 (5.3%)	0	4 (2.7%)
Dizziness	4 (11%)	5 (14%)	1 (2.6%)	2 (5.4%)	12 (8.2%)
Headache	7 (19%)	8 (22%)	7 (18%)	6 (16%)	28 (19%)
Gastrointestinal disorders					
Constipation	3 (8.3%)	2 (5.6%)	1 (2.6%)	4 (11%)	10 (6.8%)
Nausea	6 (17%)	7 (19%)	7 (18%)	9 (24%)	29 (20%)
Vomiting	1 (2.8%)	4 (11%)	3 (7.9%)	4 (11%)	12 (8.2%)
General and administrative site conditions					
Administrative site warmth	1 (2.8%)	0	1 (2.6%)	0	2 (1.4%)
Feeling hot	1 (2.8%)	2 (5.6%)	1 (2.6%)	2 (5.4%)	6 (4.1%)
Impaired healing	1 (2.8%)	0	0	0	1 (0.7%)
Infusion site pain	1 (2.8%)	1 (2.8%)	0	1 (2.7%)	3 (2.0%)
Wound dehiscence*	2 (5.6%)	5 (14%)	3 (7.9%)	5 (14%)	15 (10%)

The table provides a summary of TEAEs, including TEAEs occurring in more than 10% of subjects and TEAEs of interest or clinical importance.

*All TEAEs of wound dehiscence occurred at one clinical research site and were due to a single assessor who did not have appropriate investigator oversight and was not adequately trained to differentiate normal wound healing from abnormal wound healing. This deviation was not identified until after the database was locked.

TEAE, treatment-emergent adverse event.

the current study is about 50% greater than that of VX-548 in a similar bunionectomy model.

Although local anesthetics mitigate the immediate pain after orthopedic surgery, the duration of analgesia is limited to at most 1 to 2 days.[40] Extended-release formulations of bupivacaine have failed to extend analgesia beyond 48 h in orthopedic surgery.[16–23] Local anesthetics may block touch sensation, proprioception, and muscle strength.[41]

The minimal clinically important difference for acute postoperative pain has been reported to be about 10 mm on the 100-mm visual analog scale.[42] Although we used the 0 to 10 NRS scale in our study, the published visual analog scale data help interpret the clinical relevance of our results. The mean differences in NRS pain scores at the 48-, 96-, and 168-h assessments between the vocacapsaicin (0.30 mg/ml) treatment group and the placebo treatment group were 1.5, 1.5, and 1.1, respectively. These differences represent relative reductions in pain of 39, 50, and 49%, respectively. These reductions all reached statistical significance. As shown in figure 2, the cumulative reduction in pain over the first 96 h was 33% and was statistically significant. Taken together, these results suggest clinically useful reductions in pain with vocacapsaicin.

Vocacapsaicin is a prodrug of capsaicin, a TRPV1 agonist. Capsaicin produces sustained analgesia without loss of sensation, proprioception, or muscle strength[43,44] by activating TRPV1 receptors on C-fiber nociceptors,[45] the nerves that mediate dull, aching pain after surgery.[46] Peripheral administration of a TRPV1 agonist causes initial activation followed by defunctionalization of C-fiber nociceptors *via* selective ablation of the TRPV1-expressing efferent nerve terminals.[45] C-fiber regeneration occurs over weeks to months,[47–50] with the overall process considered analogous to pruning leaves off a tree and waiting for regrowth.[44] The 2021 Nobel Prize in Physiology or Medicine was awarded for research into the TRPV1 receptor, also called the capsaicin receptor.[45]

The initial activation of TRPV1 receptors can be readily appreciated as the burning sensation when capsaicin is consumed in spicy foods. As shown in figure 3, C-fiber activation initially increased pain in patients receiving vocacapsaicin. Infiltration of local anesthetic into the surgical site between the first and second metatarsal is standard for a Mayo block and may eliminate this early pain. This was not done in this proof-of-concept study to avoid potential drug interactions. The potential of local infiltration or regional anesthesia to effectively manage the pain of initial activation is being evaluated in subsequent studies. Encouraging preliminary results from an unpublished study evaluating local infiltration of anesthetic (results available at ClinicalTrials.gov NCT03885596) suggest that this may be the case.

Bunionectomy is a validated model for acute pain after orthopedic surgery producing moderate postsurgical pain (NRS pain score = 4 to 7) for about 48 h and is reported to have good analgesic assay sensitivity for at least 72 h.[5,29–31,51] The standardized surgical procedure is useful for proof-of-concept analgesic studies and for demonstrating effectiveness for regulatory approvals.[5,17,31] Analgesic efficacy results from bunionectomy studies are generalizable to other bony surgery, as well as soft tissue procedures.[28] Because vocacapsaicin is an aqueous solution, it can readily be delivered and evaluated in other clinical settings.

A limitation of this model, and consequently of the study, is our restricting analgesia from 0 to 96 h after surgery to opioids. This restriction does not reflect accepted practice but was imposed as part of the experimental model to provide a precise assessment of pain and opioid use through the fourth postoperative day. A further possible limitation is the extent of the range of concentrations tested: concentrations higher than 0.30 mg/ml might provide better analgesic efficacy. This can be tested in future studies.

We provided comprehensive anesthesia and analgesia at the time of surgery, so the significant early observation of 26% of patients never requiring opioids after surgery in the vocacapsaicin (0.30 mg/ml) group *versus* 5% in the placebo group will likely translate directly to clinical practice. Furthermore, after 96 h, all patients were treated with multimodal analgesia, which is typical clinical practice. Therefore, the significant reductions in pain and opioid use from 96 to 336 h (figs. 3 and 4) reflect improvement in postoperative pain management beyond what is currently possible in patients after bunionectomy.

Conclusions

The study demonstrates that vocacapsaicin (0.30 mg/ml) improves analgesia and decreases opioid use after bunionectomy in comparison to patients receiving placebo and otherwise identical perioperative anesthesia and postoperative analgesia. The benefits were evident early and throughout the 2 weeks after surgery, without evidence of local or systemic toxicity. Vocacapsaicin resulted in earlier cessation of postoperative opioids, a potential patient and public health benefit. These data suggest that intraoperative administration of vocacapsaicin may provide substantial benefits in other surgical procedures.

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Competing Interests

Dr. Shafer and Mr. Vaughn are consultants to Concentric Analgesics (San Francisco, California). Drs. Teichman and Donovan are employed by Concentric Analgesics. Drs. Shafer, Teichman, and Donovan have equity interests in Concentric Analgesics. Dr. Shafer's research program at Stanford University (Stanford, California) was partly funded through a grant from Concentric Analgesics. The work was related to vocacapsaicin development. Dr. Minkowitz has provided consulting and/or clinical research for Heron Therapeutics (San Diego, California), Pacira Biosciences (Parsippany, New Jersey), TLC (Taiwan Liposome Company, Taipei, Taiwan), Cali Biosciences (Shenzhen, China), and PainReform (Tel Aviv, Israel). Dr. Leiman has provided consulting and/or clinical research support for Pacira Biosciences, Innocoll Biotherapeutics (Princeton, New Jersey), Durect Corporation (Cupertino,

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Reproducible Science

Full protocol available at: steven.shafer@stanford.edu. Raw data available at: steven.shafer@stanford.edu.

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Supplemental Digital Content

Supplement 1. Study protocol, https://links.lww.com/ALN/D546
Supplement 2. Exploratory efficacy endpoints, https://links.lww.com/ALN/D547

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

A Musical Portrait of Lithotomy without Anesthesia

In antiquity, the Hippocratic Oath forbade untrained practitioners from "cutting for stone," or surgically removing bladder stones. More than a millennium later, anesthesia and antisepsis had yet to be discovered, and lithotomy—at the time, transperineal stone extraction—was still an excruciating and life-threatening ordeal. So intense was the agony that one French composer, Marin Marais (1656 to 1728, *right*), wrote an entire work based on either direct experience or observation. Having excelled at the viola da gamba (or viol, *right*) from his youth, Marais was appointed to Louis XIV's royal orchestra at Versailles at age 20. He would later compose for viol and harpsichord *The Portrait of the Bladder Stone Operation* (1725, *background score*), a prime example of program music—instrumental music that depicts a written narrative. *The Portrait*'s melody first ascends ominously in a somber E minor as the patient climbs into the lithotomy apparatus, then undulates as his arms and legs are tied with silks. It trembles and rises in pitch as the perineal incision is made. When forceps enter to oust the stone, the highest note in all viol literature shrills as the patient shrieks and loses his voice. An upbeat movement in E major then follows the funereal piece, celebrating the tremendous relief of the postsurgical period in the era before anesthesia. (Matloubieh *et al.* Urology 2020; 141:60–3. Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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