TRPV1 from Bench to Bedside: Vocacapsaicin Produces Durable Postsurgical Analgesia and Earlier Opioid Cessation

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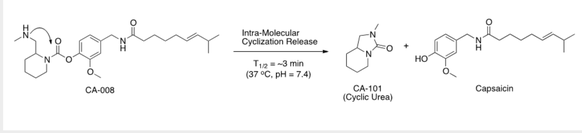
Background and Aims:

Pain management after surgery remains an unmet need.[1-5] Oral opioids remain a key part of management,[1,2] despite side effects, safety concerns, and the risk of persistent opioid use.[6-8] Treating pain at its source, the nociceptor, is considered an ideal approach.[9-12] Targeting TRPV1 in the periphery is an attractive, untapped strategy.

Brief exposure to a therapeutic dose of capsaicin, a well-studied TRPV1 agonist, causes sustained analgesia without loss of sensation, proprioception, or muscle strength,[13,14] by activating TRPV1 receptors on C-fiber nociceptors,[15] the nerves that mediate dull, aching pain.[16] Vocacapsaicin is a novel prodrug of capsaicin. Designed specifically for tissue infiltration, vocacapsaicin is more soluble and rapidly releases capsaicin following local administration[17](Figure 1).

We conducted studies in two surgical models, bunionectomy and total knee arthroplasty (TKA), to test the effect of vocacapsaicin on postsurgical pain and opioid use.

Figure 1: Vocacapsaicin: pH-labile, Water-soluble Prodrug of Capsaicin



Methods:

We completed two multicenter, randomized, double-blind, placebo-controlled, dose-optimization studies of vocacapsaicin during orthopedic surgery in bunionectomy and TKA. Vocacapsaicin doses were 0.05-0.5 mg/mL.

During surgery, patients received full standard-of-care anesthesia and analgesia and blinded local delivery of either placebo or vocacapsaicin. Patients were monitored for 96 hours after surgery at the study site and discharged on day 4. Serial safety and efficacy evaluations were performed at pre-specified times until day 29. Following surgery, NRS pain scores at rest and with ambulation were recorded serially and all rescue opioid use was documented.

The primary efficacy endpoint in both studies was analgesia calculated as the comparative area under the NRS pain at rest curves. Secondary endpoints included pain with ambulation, time to opioid cessation, and cumulative opioid use. Safety endpoints included local and systemic side effects.

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Abbreviations:
SOC = standard-of-care, OME = oral morphine equivalents

ClinicalTrials.gov Registration:
Bunionectomy NCT03599089; TKA NCT04203537

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Bunionectomy Results:*

The bunionectomy study randomized 147 patients.

During 14d (336h) after bunionectomy, vocacapsaicin 0.3 mg/mL reduced pain at rest 37% (p=0.01)(Figure 2A and Figure 4), ambulatory pain 30% (p=0.03), and opioid use 55% (p=0.001)(Figure 2B) vs. placebo. By day 5, all vocacapsaicin 0.3 mg/mL patients ceased opioids while at day 14, 8% of placebo patients remained on opioids (p=0.04)(Figure 3). The opioid use hazard ratio (HR) for placebo vs. vocacapsaicin 0.3 mg/mL was 1.8 (p=0.009).

Figure 2: Bunionectomy Results, A) NRS at Rest AUC (0-336h); B) Cumulative Opioid Consumption (0-336h)

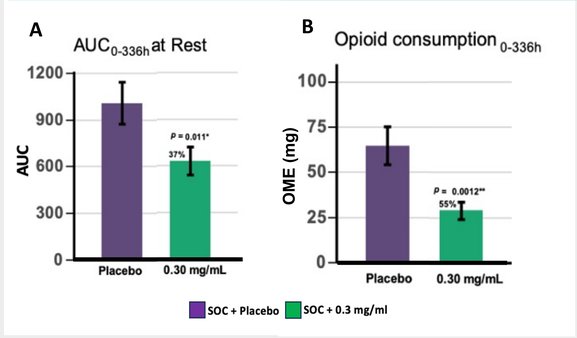


Figure 3: Opioid Cessation After Bunionectomy (Kaplan-Meier Plot)

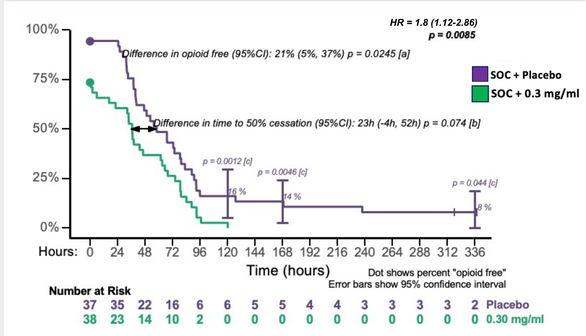
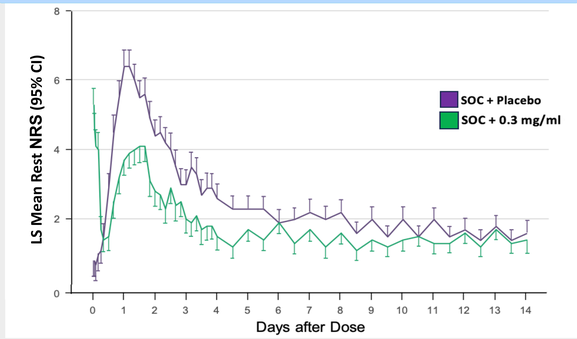


Figure 4: Mean NRS at Rest Scores (0-336h) After Bunionectomy



TKA Results:

The TKA study randomized 187 patients.

During 14d (336h) after TKA, vocacapsaicin 0.3 mg/mL reduced pain at rest 15% (p=0.03)(Figure 5A and Figure 7), ambulatory pain 14% (p=0.04), and opioid use 35% (p<0.0001)(Figure 5B). At day 15, 58% vs 38% of patients ceased opioids in the vocacapsaicin 0.3 mg/mL vs. placebo groups, respectively (p=0.02)(Figure 6). The opioid use HR was 1.8 (p=0.02). At 72h, 90% of vocacapsaicin 0.3 mg/mL patients vs. 63 of placebo patients could ambulate 30m (p<0.01)(Figure 8).

Figure 5: TKA Results: A) NRS at Rest AUC (0-336h); B) Cumulative Opioid Consumption (0-336h)

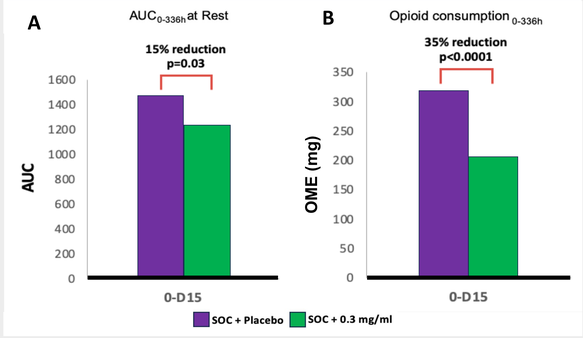


Figure 6: Opioid Cessation After TKA (Kaplan-Meier Plot)

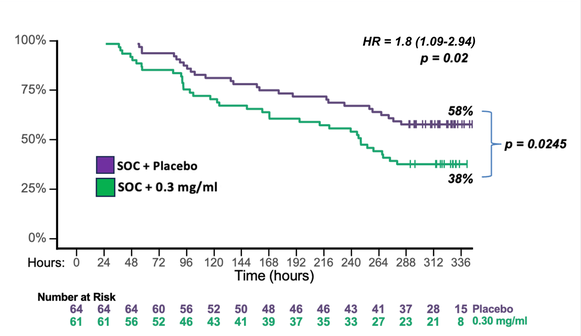


Figure 7: Mean NRS at Rest Scores (0-336h) After TKA

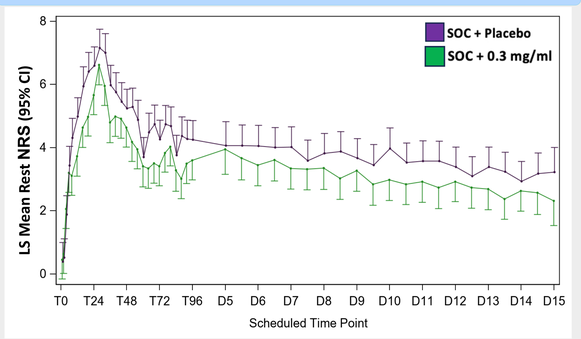
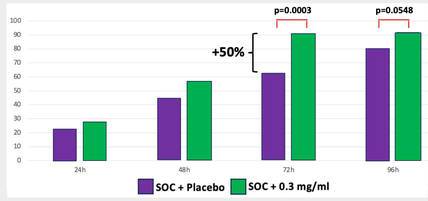
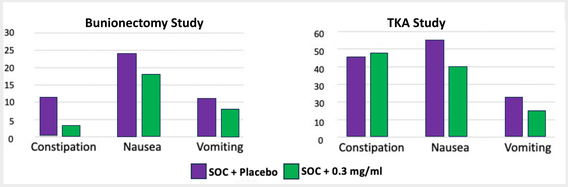


Figure 8: Proportion of Patients Able to Ambulate 100 ft Following TKA



Efficacy lasted 2 weeks after surgery, without local or systemic toxicity. A reduced GI side effects trend was seen (Figure 9).

Figure 9: Number of Patients Reporting Opioid GI Side Effects



Conclusion:

Two randomized, controlled trials in TKA and bunionectomy demonstrated that a single administration of vocacapsaicin 0.3 mg/mL during surgery improved analgesia for 2 weeks, decreased opioid use, improved functional recovery, and allowed patients to stop taking opioids sooner compared to placebo. Further studies are warranted.

Relevance for Patient Care:

This study provided evidence that TRPV1 agonism can be successfully translated into an effective postsurgical analgesic. A single intra-operative administration of the non-opioid analgesic vocacapsaicin produced clinically meaningful pain relief for two weeks following surgery and reduced the duration and quantity of oral opioid analgesic exposure. Patients in the placebo group had an HR for post-operative opioid use almost twice that of an effective dose of vocacapsaicin. This reduction of opioid use may reduce acute side effects that can interfere with recovery and may reduce persistent opioid use which has risks to both the patient and overall public health.[6-8] Intraoperative administration of vocacapsaicin may provide benefits in other surgical procedures.

Ethical Permissions:

Institutional review board approval was obtained at all sites and all patients provided written informed consent prior to study participation.

References:

1. J Pain 2016; 17(2): 131-57.; 2. JAMA Netw Open 2022; 5(12): e2248439.; 3. JAMA Surg 2023; 158(6):618-624.; 4. JAMA Surg 2023; 158(4): 378-85.; 5. N Engl J Med 2023; 389(5): 393-405.; 6. JAMA Surg 2017; 152(6): e170504.; 7. Br J Anaesth 2020; 124(5): 502-3.; 8. JAMA Surg 2020; 155(12): 1169-71.; 9. Nat Rev Drug Discov 2009; 8(1): 55-68.; 10. Anesthesiology 2007; 107(3): 369-71.; 11. Anesth Analg 2008; 107(1): 282-91.; 12. JAMA Surg 2022; 157(6): 481-9.; 13. Br J Anaesth 2011; 107(4): 490-502.; 14. Front Neurol 2022; 13: 998904.; 15. Nature 1997; 389(6653): 816-24.; 16. Anesthesiology 1988; 68(4): 571-90.;17. Pain 2014; 155(3): 441-56.