TITLE:

Vocacapsaicin reduces pain and opioid consumption for two weeks following a single administration during total knee arthroplasty

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BODY:

Introduction:
Multi-day postoperative analgesia following total knee arthroplasty (TKA) remains an important unmet medical need. Vocacapsaicin (formerly CA-008) is a prodrug of capsaicin, a TRPV1-agonist that selectively desensitizes pain-conducting nerve fibers without producing sensory numbness or motor weakness. We previously demonstrated that a single administration of vocacapsaicin produced postsurgical analgesia and reduced opioid consumption (OC) for two weeks following bunionectomy.[1] We sought to replicate these results in a randomized double-blinded multicenter study of patients undergoing TKA.

Methods:
The study was conducted in patients undergoing primary TKA under spinal anesthesia with full standard-of care perioperative analgesia including ropivacaine 200 mg (femoral nerve block, IPACK and periarticular infiltration) and intraoperative acetaminophen and ketorolac (ClinicalTrials.gov: NCT04203537). Eligible subjects were aged 18-80, BMI up to 42 kg/m2. Patients were excluded if opioid tolerant, allergic to capsaicin, or had a concurrent painful condition. Following IRB approval and written informed consent, consenting patients were randomized to placebo, 36 mg, or 60 mg of vocacapsaicin in 120 ml of normal saline. The test article was instilled onto cut bone surfaces, infiltrated into peri-articular tissue, and injected into the closed capsule at the end of the case. Postoperative pain and analgesic consumption were recorded in hospital for 4 days, and after hospital discharge for at least two weeks following surgery. After discharge, all subjects received celecoxib twice daily and acetaminophen or acetaminophen/oxycodone as needed.

The primary efficacy endpoint was the area under the curve (AUC) of the Numerical Rating Scale at rest from 0 to 96 hours (NRS-R $AUC_{0\text{-}96h}$). Secondary efficacy endpoints included evoked pain with activity (NRS-A $AUC_{0\text{-}96h}$), total opioid consumption ($OC_{0\text{-}96h}$), and the time of discontinuation of opioid use (DO). Exploratory endpoints included measures of recovery during

hospitalization and NRS-R, NRS-A and OC from 96 hours to Day 15. Safety endpoints included vital signs, physical examination, surgical site assessments, neurosensory testing, adverse events, and clinical laboratory evaluations.

Results:

A total of 193 patients (mean age 62.3 years) were enrolled at 4 sites from December 2019 to September 2020. Groups were well-matched at baseline. Over the first 4 days, vocacapsaicin 36 mg met the primary and secondary endpoints for both pain and opioid consumption. The NRS-R $AUC_{0\text{-}96h}$, was reduced by 17% ($p=0.0012$). The NRS-A $AUC_{0\text{-}96h}$ was reduced by 20% ($p=0.0006$). $OC_{0\text{-}96h}$ was reduced by 30% ($p<0.0001$). Vocacapsaicin enabled earlier ambulation during hospitalization and produced a trend towards earlier DO.

Reductions in pain and opioid use continued over the 2 weeks following surgery. Vocacapsaicin 36 mg reduced NRS-R $AUC_{0\text{-}15d}$ by 15% ($p=0.03$) and NRS-A $AUC_{0\text{-}15d}$ by 14% ($p=0.04$). Opioid consumption following discharge, $OC_{96h\text{-}15d}$ was reduced by 52% ($p=0.0063$). Overall opioid consumption, $OC_{0\text{-}15d}$ was reduced by 35% ($p<0.0001$). An analgesic effect was still evident on day 15. Vocacapsaicin 36 mg was more effective than vocacapsaicin 60 mg. Both doses of vocacapsaicin generally appeared safe and well-tolerated. No local or systemic safety concerns were observed.

Discussion:

Vocacapsaicin provided durable and clinically meaningful analgesia following TKA, including reduced pain and opioid consumption at remarkably high levels of statistical significance. Vocacapsaicin also improved functional recovery. The reduction in the amount and duration of opioid use helps address the unmet medical need for effective non-opioid postsurgical analgesia by reducing or potentially eliminating the requirement for opioids following hospital discharge. Further studies will confirm and expand the potential of vocacapsaicin for prolonged postsurgical analgesia.

References:

1. Gottlieb IJ, Beaton A, Solanki D, et al. A randomized, placebo-controlled trial of intraoperative administration of CA-008 for post-operative analgesia after bunionectomy. Presented at ASRA 2019. (https://epostersonline.com/ASRASPRING19/node/1194?view=true)