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Research Article

Analgesic Effects of Vanilloid Receptor Desensitization by Capsaicin in the Oral Surgery Model

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Abstract

Capsaicin, a member of the vanilloid class, binds to the Transient Receptor Potential Channel-Vanilloid Subtype 1 (TRPV-1), a Ligand-Gated Calcium Ionophore commonly known as VR-1 producing a selective activation followed by ablation of pain specific neurons. The analgesic potential of local administration of capsaicin as a prototype of the vanilloid class was evaluated post-operatively in the oral surgery model of acute pain. Subjects in this double-blinded, placebo and positive controlled trial randomly received placebo or capsaicin 24 hours prior to oral surgery and ketorolac or placebo immediately prior to surgery. The dose of capsaicin was chosen to minimize discomfort following the injection (24 hours prior to tooth removal) that might permit patients to identify which treatment group they had been assigned to. One impacted third molar was removed and patients rated their pain every 20 minutes for a total of 240 minutes and then at home at 12, 24, and 48 hours using a 100 mm VAS. The capsaicin group reported significantly less pain compared to the placebo group at the 60, 80 and 100-minute observations after surgery. There was no significant difference between groups at the 12, 24, and 48-hour observations post-operatively. Rescue medication usage was similar among all three groups. There were a greater percentage of patients without side effects in the capsaicin group.

These data indicate that 100μg capsaicin demonstrates [6] analgesic activity in a clinical model predictive of analgesia for vanilloid receptor ablation in humans. The relatively short duration of analgesia may be due to incomplete receptor inactivation due to dose-limiting discomfort initially produced by sub-mucosal administration of capsaicin and the contribution of other nociceptive fibers over time not containing TRPV1 receptors.

Introduction

Vanilloids are a group of small organic compounds that bind to the Transient Receptor Potential Channel-Vanilloid Subtype 1 (TRPV1) receptor, a Ligand-Gated Ionophore commonly known as VR-1 [2] Activation of TRPV1 is important for noxious-mediated thermal stimuli and inflammatory responses [2,5,30]. The initial activation of the TRPV1 receptor in the periphery leads to release of neuropeptides such as substance P (SP) and Calcitonin-Gene Related Peptide (CGRP) [15,19] that promotes aggregation of inflammatory mediators and markers [14,31,32] to activate nociceptive pathways in the trigeminal system and spinal cord.

This initial reaction is followed by a period of desensitization; C-fibers and some a fibers degenerate during this period and a significant loss of small diameter sensory neurons is associated

with desensitization [2]. Prolonged exposure to TRPV1 agonists results in depletion of TRPV1 receptors, contributing to a long term desensitization of nociceptors resulting in analgesia.

The TRPV1 receptor has been cloned [3] thus allowing for exploration of small molecules for this therapeutic target. Capsaicin, a derivative of vanillyl-amide, 8-methyl-N-vanillyl-6-nonenamide belongs to the vanilloid group and is the main ingredient in hot pepper [15]. Humans demonstrate a decrease in sensitivity to painful stimuli after intradermal or topical administration of capsaicin that initially provokes a burning sensation [27-29]. During this phase the individual is refractory to certain painful stimuli [16]. This period of insensitivity is, in animal models, dependent on dose, route of administration, and age at time of administration. Topical capsaicin has been shown to be effective in the treatment of neuropathic pain, trigeminal neuralgia, post-herpetic neuralgia and oral mucositis [1,9,25].

The property of vanilloids to desensitize nociceptors and to decrease chronic pain suggests the ability to attenuate nociceptor transmission when given preemptively. Preemptive analgesia can be narrowly defined as an intervention that is given prior to tissue injury to block acute inflammation and pain postoperatively following anesthetic offset. Preventive analgesia is a more generalizable concept including both preoperative and postoperative interventions [11-13] to attenuate the onset of acute inflammation leading to sensitization and hyperalgesia. This led us to evaluate the potential of capsaicin for preventive analgesia in the oral surgery model, a well characterized clinical paradigm for studying analgesics [4,7,13] and preemptive analgesia [12,17]. Previous studies in the oral surgery model indicate that pain reported at 48 hours post-operatively is sensitive to anti-hyperalgesic manipulations including local anesthetic blockade prior to oral surgery [12], local anesthetic blockade immediately following oral surgery [11], and perioperative dextromethorphan administration [13]. We hypothesized that prior capsaicin administration would reduce the initial nociceptive barrage that occurs after local anesthetic offset that otherwise contributes to sensitization and the development of hyperalgesia. This study evaluates the analgesic effects of capsaicin administered prior to oral surgery on pain in the immediate post-operative period and the anti-hyperalgesic effects at 48 hours.

Methods

Healthy volunteers (n=140) between the ages of 16-40 were evaluated at the National Institutes of Health (NIH) Pain Clinic for surgical removal of one mandibular third molar. Inclusion criteria consisted of a surgical extraction of a soft tissue impacted or partial bony impacted third molar and an American Society of Anesthesiologists (ASA) physical status of 1 or 2. Exclusion criteria consisted of pregnant or breast feeding females, allergy to the investigational drug or red chili peppers, chronic use of analgesics (NSAIDS, opioids, steroids, antidepressants, anticonvulsants) or presence of chronic disease. Informed consent was obtained from all subjects. The National Institutes of Dental and Craniofacial Research (NIDCR) Institutional Review Board approved the clinical protocol.

Patients were allocated into placebo, capsaicin and ketorolac groups in a skewed randomization. Ketorolac was used as a positive control since it provides profound analgesia when given intravenously for tooth extraction [24].The drugs were formulated, blinded and randomized by the NIH Pharmaceutical Development Service. Capsaicin dosage was determined by a prior dose range pilot study [21] indicating that 100 µg was active but with minimal patient reports of burning pain at the time of drug administration. A double dummy design (Table 1) for treatment delivery was used.

Drug group	Sub mucosal Injection	Intravenous injection
Capsaicin	Capsaicin 100 µg	Saline
Placebo	Carrier	Saline
Ketorolac	Carrier	Ketorolac 30mg

Table 1: Double dummy design

The combination of capsaicin plus ketorolac was not evaluated as 30 mg of ketorolac reliably reduces the level of pain postoperatively to 'slight pain' making any additional analgesic effect difficult to detect (Figure 2). Resinifera Toxin (RTX) was not used due to ethical concerns about the possible effects of long-term TRPV-1 ablation on postoperative healing.

The two arms consisted of capsaicin 100 µg administered by sub-mucosal injection 24 hours prior to the procedure or ketorolac 30 mg intravenously administered prior to tooth removal. On the day before surgery, patients were given local anesthetic (0.5% bupivacaine with epinephrine 1:200,000) and then received a submucosal injection of capsaicin or vehicle at the clinic. Patients were given acetaminophen 325 mg to be taken as needed for pain at the clinic or at home following the injection.

On the day of the surgery, patients returned to the clinic where they received an intravenous injection of ketorolac or saline. Patients were sedated with midazolam 2 to 5 mg intravenously and intraoral local anesthetic injections of 2 % lidocaine with epinephrine (1:100,000) were administered. Pain was evaluated using a 100 mm Visual Analogue Scale (VAS) anchored by 'no pain' and 'Worse Pain Imaginable' every 20 minutes until the patient requested rescue medication or 4 hours had passed following surgery. Rescue medication (acetaminophen 975 mg with codeine 30-60 mg) was given if the pain was moderate and ≥ 30 mm on the VAS. If pain was not controlled, the patient was given IV ketorolac and their data excluded. Patients recorded pain levels using VAS

in supplied pain diaries at home at 12, 24, and 48 hours as soon as they woke up, before taking any analgesics (acetaminophen or codeine). In addition, patients recorded acetaminophen and codeine tablet usage at home as well as adverse events. Patients returned 48 hours after surgery to return all pain diaries and unused medications (Figure 1).

Figure 1: Timeline of procedures

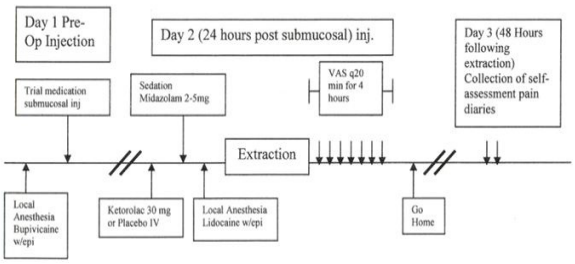

Figure 1: Timeline for administration of capsaicin on the day prior to surgery, administration of adjunctive drugs on the day of oral surgery and collection of pain intensity data over the first four hours postoperatively and at the later time points after subjects left the clinic.

A sample size of n= 130 was calculated based on an alpha value of 5%, power of 0.80 and a 45% difference between the placebo and positive control group. Data was analyzed using the SPSS statistical software package (SPSS, Inc., Chicago, IL). Pain intensity over the 4-hour postoperative period was evaluated using a repeated measures analysis of variance for differences in VAS scores between the three groups. In addition, individual time points were measured using a one-way analysis of variance to establish if there was significant difference between the three groups at different time points. The measures that were performed at 12, 24, and 48 hours were treated independently due to the possible confounding influence of differing use of acetaminophen and codeine between groups and analyzed using a one-way analysis of variance. The number of acetaminophen and codeine tablets and adverse events were analyzed by Chi-square analysis.

Results

A total of 12 patients did not complete the study. Two patients (one from the capsaicin and one from the placebo group) were excluded because of severe pain and were administered ketorolac rescue medication. Five patients were lost to follow up. Three patients had medication errors and 2 patients were excluded at the time of surgery due to unanticipated difficult extractions. The study sample consisted of similar characteristics in regards to age, sex, height and weight (Table 2).

	Age	Male	Female	Height (cm)	Weight (kg)	Surgical score	Midazolam (mg)	Lidocaine (mg)
Placebo ± Std Error	22.3 ± 0.7	18	34	169.1 ± 1.2	69.9 ± 2.3	2.6 ± 0.1	4.5 ± 0.2	90 ± 3.6
Ketorolac ± Std Error	22.3 ± 1.1	10	15	169.4 ± 1.8	76.3 ± 3.9	2.7 ± 0.1	4.7 ± 0.1	90 ± 3.6
Capsaicin ± Std Error	22.0 ± 0.6	19	32	169.6 ± 1.4	73.5 ± 3.2	2.7 ± 0.1	4.5 ± 0.1	90 ± 2.5

Table 2: Demographics

In addition, intraoperative and perioperative parameters such as local anesthetic used and surgical difficulty were similar in all three groups. The similarities between groups in these risk factors for postoperative pain suggest that outcomes are related to the investigational treatments.

A slightly greater number of acetaminophen tablets were used in the capsaicin group (mean = 1.9 +/- 0.3) between the time of sub mucosal injection and operative day (Table 3) than were used in the placebo group (mean = 0.9 +/- 0.2) or the ketorolac group (1.0 +/- 0.3). Pain onset was reported during the first 60-120 minutes post-operatively as the local anesthetic effects dissipated, reached levels comparable to the verbal descriptor “Moderate” pain by 2 hours in the placebo and capsaicin groups, and remained at this level over the last two hours of the observation period (Figure 2).

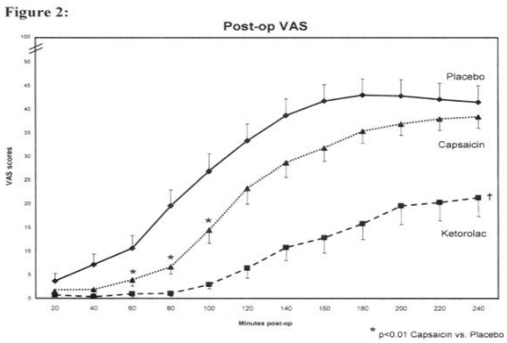

Figure 2: Pain intensity data as measured on a 100mm visual scale (VAS) every 20 minutes.

The ketorolac group reported pain comparable to 'slight pain' over the four observation period, consistent with its profound analgesic effects for acute pain in this model. For the first hours postoperatively. *p<0.05 capsaicin compared to placebo: (dagger symbol) P<0.01 ketorolac vs. placebo, capsaicin.

Pain intensity over the 4-hour period differed significantly among the three groups ($F = 14.668$, $p < 0.001$). Pain intensity was significantly lower in the ketorolac group as compared with the placebo ($p<0.001$) and capsaicin ($p<0.005$) groups over the four-hour postoperative period. Capsaicin significantly suppressed pain intensity in comparison to the placebo group ($p<0.05$) at several observations during the initial four hours following surgery. There were similar amounts of acetaminophen and codeine tablets used among the three groups during the post-operative period (Table 3).

Type of Medication	Placebo	Ketorolac	Capsaicin
Pre-op Acetaminophen	0.9 ± 0.2	1.0 ± 0.3	1.9 ± 0.3
Post-op Acetaminophen	9.0 ± 0.9	10.2 ± 1.5	10.3 ± 1.1
Post-op Codeine	4.5 ± 0.6	4.3 ± 1.0	4.1 ± 0.4

Table 3: Tablet usage for Preoperatively and Postoperatively

At the 12, 24 and 48 hour observations, there was an overall trend for the capsaicin group to have lower VAS scores in comparison to the ketorolac and placebo groups, but no significant difference was observed (data not shown).

A greater percentage of patients did not report any side effects in the capsaicin group in comparison to the placebo and ketorolac groups. The most common side effects that were reported were drowsiness, nausea, vomiting and headache. Among the side effects that were present, capsaicin had lower or similar side effects profiles in comparison to placebo and ketorolac except for vomiting (Table 4).

Side Effects	Placebo n=52 (%)	Ketorolac n=25 (%)	Capsaicin n=51 (%)
None	9 (17)	5 (20)	19 (37)
Drowsiness	37 (71)	14 (56)	23 (45)
Dizziness	6 (12)	1 (4)	4 (8)
Headache	11 (21)	5 (20)	5 (10)
Nausea	9 (17)	5 (20)	8 (16)
Vomiting	1 (2)	1 (4)	5 (10)
Other	3 (6)	8 (32)	10 (20)

Table 4: Adverse Drug Effects

Discussion

Topical capsaicin has been shown to be of benefit for chronic pain from osteoarthritis, psoriasis and diabetic neuropathy [20]. Capsaicin at the 100 μg dose in the present study demonstrated an analgesic effect for acute pain in the immediate post surgical period but had little effect at the later time points in a sensitive analgesic model. This suggests efficacy for preemptive effects on acute pain but with modest activity for the dose used.

The oral surgery model is an optimal clinical model for studying acute and preemptive analgesia. Careful patient selection minimizes variability between groups in the demographic characteristics of the subjects, surgical difficulty or the surgical procedure. In addition, confounding factors such as adjunctive medications are very similar between groups and patients with chronic illnesses that may limit the validity of results are excluded. Thus, the differences between treatments and the magnitude of the analgesic effect demonstrated likely are representative for the efficacy of the maximally tolerated dose of capsaicin used.

The magnitude and duration of the analgesic response to this dose may be due to several reasons. First, the capsaicin dose was limited due to initial discomfort at the time of the drug administration. In a pilot study [21], the capsaicin dose was selected based on patient report of a burning sensation in the vicinity of the administration site. This subjective sensation may have provided a clue to subjects as to which group they were assigned to, but the study staff performing the clinical procedure and postoperative data collection were not aware of the subjects response to the capsaicin administration on the day prior to surgery. The dose that was used in this study was to minimize this side effect and limited our ability to evaluate if greater efficacy occurs with higher doses. In addition, previous studies have demonstrated that greater effects are achieved by multiple application of capsaicin that leads to parallel loss of epidermal nerve fibers and pain sensation [23]. Even with

single administration at this dose, there was a significantly greater number of acetaminophen tablets used during the pre-operative period by the capsaicin group in comparison to the groups not receiving capsaicin. However, there was no difference in acetaminophen or codeine usage among the groups post-operatively. The difference observed in acetaminophen usage during the pre-operative period is attributed to the irritation by capsaicin at the site of administration. In contrast, there were an overall lower number of side effects that was associated with the capsaicin group in comparison to the placebo and ketorolac groups post-operatively.

Second, the sub mucosal injection of capsaicin was unable to be concentrated in the area for an extended period of time due to the delivery method. Inactivation of the TRPV1 receptor may not only be influenced by repeated administrations but also may be due to factors such as period of stimulus and increased activation of different signaling pathways that may decrease the effectiveness of desensitization of the TRPV1 receptor [18].

This study serves as a proof of concept for the potential of inactivation of the vanilloid receptor leading to a decrease in acute post-operative pain. The therapeutic potential for other vanilloid receptor agonists such as Resinifera Toxin (RTX) has been demonstrated in preclinical models [22]. The shortcomings of capsaicin (dose limitation, local burning) may be overcome by investigational small molecules that permit greater vanilloid receptor inactivation with chronic administration. There are several vanilloid receptor antagonists that have shown promise in preclinical models using this mechanism [8,10,26]. The mechanism of action of vanilloid receptor inactivation also provides other possibilities for analgesia through peripheral administration at other sites.

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