A Randomized Control Trial of Oral Capsaicin for the treatment of Pain associated with Oral Mucositis in BMT Patients

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A. Study Purpose and Rationale

The purpose of this study is to investigate whether capsaicin, the active ingredient in chili peppers, given in a candy vehicle, is effective at relieving the pain associated with oral mucositis (OM) in patients undergoing bone marrow transplant (BMT.)

OM (ulcerated oral cavity and throat) afflicts up to 40% of patients receiving chemo or radiation, and up to 76% of bone marrow transplant patients (Sonis et al. 1989.) The pain of mucositis ranges from mild to excruciating, and frequently contributes to inadequate caloric intake and compromised nutritional status. Numerous strategies have been employed in an attempt to prevent or minimize chemo-induced mucositis. Despite initially promising results, none has had a dramatic impact, and none can be considered routine therapy. Treatment of mucositis is basically supportive and palliative, consisting of a combination of oral care, mucosal protectants, topical anesthetics, and systemic analgesics. Evidence supporting benefit for any of these interventions is weak (Worthington et al, 2002.) Topical anesthetics provide relief for a short duration only and block taste perception, which may diminish the sensory quality of eating and further compromise nutritional status. Systemic opioid analgesics often produce additional side effects such as lethargy, nausea, and constipation.

Oral desensitization using capsaicin, the active ingredient in chili peppers, in a candy vehicle, may be able to provide a method of pain control for patients with mucositis, without the side effects of the other treatments. Capsaicin applied to skin or mucous membrane produces a burning sensation; repeated applications produce less burning, a process called desensitization. It is thought that this phenomenon might be useful in the treatment of pain. Indeed, Berger, et al. published data revealing substantial pain reduction in a series of 11 patients with OM pain from cancer therapy treated with capsaicin candies (1994.)

This study will be undertaken to investigate whether these promising results can be replicated in a randomized, controlled setting. Identification of an effective method of pain control for patients with mucositis would be a huge step forward in the management of patients undergoing chemotherapy treatment, and could potentially impact nutritional status in these patients as well.

B. Study Design and Statistical Analysis

This is a prospective randomized control trial that will take place over approximately one year. Patients undergoing BMT at Columbia University Medical Center who develop grade 2, 3 or 4 mucositis, as defined by the ECOG (Easter Cooperative Oncology Group) assessment, will be approached to enroll in the study. Upon enrollment they will be randomized via computer generated methods to either the treatment or control arm.

Patients will be asked to report their pain verbally on a 0-10 intensity scale, 0 being no pain, and 10 being the most intense pain ever experienced, three times daily throughout the study. Numerical Rating Scales such as this have been shown to be particularly effective at identifying response of pain to intervention, and Jensen et al. showed that frequent assessments increase the reliability and validity of pain intensity measurement in patients with ongoing pain (1993.) Given the current lack of effective pain control for this syndrome, a reduction by 2 points on a numerical rating scale would be considered clinically desirable. As experience and reporting of pain varies significantly from person to person, standard deviation is likely to be substantial. Power analysis was therefore performed estimating an effect

of 2 and a standard deviation of 4. Using these parameters, it was determined that this study requires a total of 128 subjects, 64 in each arm. Statistical analysis will be performed using an unpaired t-test with alpha of 0.05 and beta of 0.80. Should the results fail to fall in a normal distribution, statistical analysis will be performed using the Wilcoxon Rank Sums Test.

C. Study Procedure

Adult patients (age =18 or greater) who are undergoing bone marrow transplant at Columbia University Medical Center will be evaluated daily for the development of oral mucositis by a trained research assistant. Those patients who meet criteria for grade 2 ("painful erythema, edema or ulcers, but can eat,") grade 3 ("painful erythema, edema or ulcers, and cannot eat") or grade 4 ("requires parenteral or enteral support") mucositis will be asked to participate. Should a patient choose to enroll, he will be randomized to either the treatment arm or the control arm via a computer-generated method. Those patients in the treatment group will receive capsaicin candies prepared according to a standard recipe. Those in the control arm will receive a similar candy that substitutes black pepper for capsaicin, to simulate a burning sensation without desensitization of the neurons.

Patients will be asked to rate their pain verbally on a 0-10 intensity scale, 0 being no pain and 10 being the most intense pain ever experienced. Patients will be asked to rate their average pain over the previous 8 hours three times, eight hours apart, prior to first treatment. After the third assessment, treatment with one candy every 4-6 hours will be initiated. Patients will continue to rate their pain every eight hours for four consecutive days. At the end of four days, patients will be given the option of continuing treatment, but no further data will be collected. The primary outcome measured will be the patient's average daily pain rating as compared to pre-treatment rating. Secondary outcomes will include caloric intake and need for additional systemic analgesia. Data will be recorded by either the supervising physician or a research assistant.

Patients may refuse a candy at any time during the study for any reason. At no time will other methods of pain control be withheld from patients, and they may continue to ask for other routinely used therapies including "magic mouthwash" and systemic analgesia on an as needed basis.

D. Study Drugs

All of the ingredients in both the treatment and placebo candies are standard household items, and are therefore not subject to FDA approval. Currently, clinical use of capsaicin involves topical application in a cream for the treatment of stump pain, post-herpetic neuralgia, acute herpes zoster, and post-mastectomy pain. Capsaicin cream is commercially available in two strengths: 0.025% and 0.075%.

***Treatment*:** Capsaicin will be placed in a standard taffy recipe, identical to that used by Berger et al. Taffy is considered a good vehicle because it lacks sharp edges, which could exacerbate mucositis pain. Furthermore, dissolution over several minutes provides sufficient exposure to capsaicin to produce desensitization. Finally, sucrose and tactile stimulation have both been shown to minimize the initial burning discomfort of capsaicin (Karrer et al. 1991, Green 1986.) Each candy will contain approx 5-9 ppm, a concentration thought strong enough to produce desensitization without burning so much as to be intolerable.

Aside from the predicted burn, few side effects are predicted. In Berger's series, one patient with known hemorrhoids experienced burning hemorrhoids.

Recipe for Capsaicin Candies: to be made by ICCR's Research Kitchen – adapted from Joy of Cooking Cookbook:

- 1-cup sugar
- 3/4-cup light corn syrup
- 2/3-cup water

- 1 tbsp cornstarch
- 2 tbsp butter
- 1tsp salt
- 2 tsp vanilla
- 1/2 tsp cayenne pepper (McCormick and Company, Inc.)

Combine all ingredients except vanilla and cayenne pepper and cook over medium heat, stirring constantly to the hard ball stage. Remove from heat, stir in vanilla and cayenne pepper. When cool enough to handle, pull taffy. When stiff, pull into strips, cut into 1-inch pieces, and wrap. Makes approx 1 lb of candy.

***Placebo*:** The placebo will be made with an identical recipe, substituting black pepper for the cayenne pepper, to stimulate a burning sensation without desensitizing the neurons.

The dosage schedule of 1 candy every 4-6 hours was determined based on Berger's observation that most patients required 4-6 candies per day to maintain pain relief (1994.)

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Study Subjects

***Inclusion criteria*:**

- Adult patients aged 18 or greater
- undergoing BMT in a protocol at CUMC
- whose PI has given permission for participation in this study
- evidence of Grade 2, 3, or 4 oral mucositis as defined by ECOG scale.

***Exclusion criteria*:**

- Any patient with known intolerance to red pepper, cayenne pepper, or black pepper, or any of the other ingredients in the candy vehicle, including sugar, light corn syrup, cornstarch, butter, salt, and vanilla extract.
- Anyone whose mental status prevents them from understanding how to report pain on a 0-10 intensity scale.

H. Recruitment of Subjects

Patients undergoing Bone Marrow Transplant in one of Columbia University Medical Center's protocols, meeting criteria for grade 2-4 mucositis as defined by ECOG, whose BMT protocol PI and primary oncologist has given permission for participation, will be approached about participating by either the supervising physician or a trained research assistant.

I. Confidentiality of Study Data

Study data will be coded and stored in a secure location, in accordance with IRB regulations.

J. Potential Conflict of Interest

none

K. Location of the Study

CUMC oncology ward

L. Potential Risks

Potential risks include discomfort caused by the burning sensation produced by capsaicin. There is also the risk that the patient may receive placebo rather than active treatment. It is unlikely that the patient's condition may worsen as a result of either the treatment or the placebo, but the natural course of oral mucositis may worsen before improvement, and therefore it may appear as such. Patients with known hemorrhoids may experience burning hemorrhoids.

M. Potential Benefits

Potential benefits may include relief of the pain associated with oral mucositis. Participation in this study may also help identify an effective method of pain control for patients undergoing BMT with mucositis, and could therefore benefit future BMT recipients.

N. Alternative Therapies

If a patient does not wish to participate, alternatives include those previously mentioned therapies, which are used empirically, including topical anesthesia and systemic analgesia alone without an additional experimental treatment.

O. Compensation to Subjects

none

P. Costs to Subjects

none

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

N/A