A221304

A Phase III Placebo-Controlled, Randomized Three-Arm Study of Doxepin and a Topical Rinse in the Treatment of Acute Oral Mucositis Pain in Patients Receiving Radiotherapy With or Without Chemotherapy

ClinicalTrial.gov Identifier: NCT02229539

Study Background

Trial Description

The purpose of this study is to test whether a mouthwash made with a drug called doxepin can reduce the pain caused by mouth sores resulting from radiation therapy. A number of mouth rinse preparations exist for patients with treatment-related oral mucositis pain such as the DLA rinse, an over-the-counter medication. This study will evaluate the effects of doxepin compared to DLA (diphenhydramine, lidocaine and antacids) and placebo. Doxepin is approved by the Food and Drug Administration (FDA) for the treatment of depression, anxiety, long-term pain management, as well as management of rash.

Arms:

Doxepin rinse: (Experimental): Patients receive 2.5 mL (25 mg) doxepin and 2.5 mL water orally, swish and gargle for 1 minute then spit. Doxepin rinse is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients randomized to doxepin or placebo, they and their caregivers will continue to be blinded to the treatment. Patients will complete the Oral Symptoms booklet per the protocol.

DLA (diphenhydramine, lidocaine and antacid) rinse: (Active Comparator): Patients receive 5.0 mL DLA orally, swish and gargle for 1 minute then spit. DLA is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave

the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients receiving DLA during the continuation phase of the study, they and/or caregivers may be aware that they are receiving DLA. Patients will complete the Oral Symptoms booklet per the protocol.

Placebo rinse: (Placebo Comparator): Patients receive 2.5 mL placebo and 2.5 mL water orally, swish and gargle for 1 minute then spit. The placebo rinse is administered in the clinic on Day 1 (Cycle 1). The patient will remain at the treating location for the first hour and complete the Oral Symptoms booklet at time zero (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. There is an optional continuation phase within seven days following Day 1 (Cycle 1), patients will be encouraged to continue treatment with the study agent for an additional week (Cycle 2) where the patient takes the rinse at home every 4 hours. Chemotherapy is allowed during the continuation phase. Patients randomized to doxepin or placebo, they and their caregivers will continue to be blinded to the treatment. Patients will complete the Oral Symptoms booklet per the protocol.

Objectives:

Patients are stratified according to sex (male vs. female), concurrent use of chemotherapy (no vs. yes), patient age at registration (< 60 years old vs. ≥ 60 years old and RTOG acute radiation morbidity criteria (1 vs. 2 vs 3 or more). Protocol therapy will consist of 2 cycles. Patients are randomized to one of three treatment regimens, which include doxepin, DLA and placebo. Cycle One will consist of one day. The care provider or nurse will confirm that the oral pain is at least 4 out of 10 severity level at the time of the rinse on the first day of the study. If the pain score is less than 4 then administration will be delayed until the pain is at least 4. Patient will be asked to complete the Oral Symptoms booklet at baseline (prior to the oral swish, gargle and spit), and at 5, 15, 30 and 60 minutes post-administration. After completing the booklet at 60 minutes, patients may then leave the clinic and complete the 2- and 4-hour assessments at home. Cycle Two will consist of an optional continuation phase lasting up to 7 days. Initiation of the Cycle 2/Continuation Phase may be delayed up to one week after Cycle 1/Day 1.

Primary Objective:

1. Determine whether the doxepin rinse or DLA rinse is more effective than placebo in reducing OM-related pain in patients undergoing RT to the oral cavity, as measured by a patient-reported questionnaire at baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, 2hours, and 4 hours.

Secondary Objectives:

1. Assess the adverse event profile of the doxepin rinse, the DLA rinse agent, and the placebo using a patient-reported questionnaire at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours for domains of unpleasant taste, burning or stinging discomfort, and drowsiness.

2. Compare the incidence of using additional analgesics between 1 and 4 hours after the initial mouthwash, between the doxepin oral rinse, the DLA rinse agent, and the placebo arms.

3. Compare the length of time that each study product is used by patients in the one-week continuation phase.

4. Compare the daily pain scores in the one-week continuation phase for the three study arms.

5. Compare the 24-hour morphine equivalent dose used in the continuation phase for the three study arms.

Study Milestones:

Start date: November 2014

Primary Completion Date: May 2016

Publication Information:

Analysis Type: Primary

Pubmed ID: 30990550

Citation: JAMA. 2019 Apr 16;321(15):1481-1490. doi: 10.1001/jama.2019.3504.

Associated Datasets:

NCT02229539-D1-Dataset.csv (Fig1_allptchar),

NCT02229539-D2-Dataset.csv (Anlypt),

NCT02229539-D3-Dataset.csv (c1ctcae),

NCT02229539-D4-Dataset.csv (c2ctcae)

Dataset Information:

Dataset Name: NCT02229539-D2-Dataset.csv (Anlypt)

Description: Dataset NCT02229539-D2-Dataset.csv (Anlypt) is one of 4 datasets associated with PubMed ID 30990550. This dataset contains information that will allow you to reproduce the primary analysis.

Unless noted in the comments, missing elements indicate the data was not collected for the patient.

NCT02229539-D2-Dataset.csv (Anlypt) Data Dictionary:

LABEL	NAME	elements	comments
Patient Reference	PATREF		
Continuation Phase Treatment Status	cont_phase_status	Available for continuation phase analysis, Discontinued at end of chemotherapy cycle 1	
Arm	ARM	Doxepin, Placebo, DLA	
Age (years)	AGE		To protect health information, patients aged 90 years or older are categorized as ">=90".
Age Group	AGE_G	>=60 years old, <60 years old	
Race	RACE1	White, Asian, Black or African American, Not reported: patient refused or not available	
Gender	GENDERC	Female, Male	
Concurrent chemotherapy	CHEMUSE	Yes, No	

Mucous membrane score	MMSCORE	3 or more, 2, 1	
ECOG performance status	ECOGPS	1, 0, 2	
Oral pain score at registration	PAIN_SC	4, 5, 6, 7, 8, 9, 10	0-10 scale with 0=No pain; 10= Worst pain imaginable or possible
Baseline: Currently Smoke Cigarettes	c1v0_SMOKE	No, Yes	
Baseline: Drink Alcohol	c1v0_DRINK	No, Yes	
Day 1 Total Pain (AUC)	c1pain_area		Cycle 1 Day 1 Total pain score during the first 4 hours after treatment (using the mean score as measured by the area under the curve and adjusted for the baseline pain score) There was a typo in the publication (first paragraph of page 1486) for the following sentence: • the placebo mouthwash group (median, 8.7 points [IQR, 2.0-13.0 points], P = .02) 8.7 points is the mean and the correct median is 6.8 points.
Day 1 Drowsiness (AUC)	c1drowsiness_area		Cycle 1 Day 1 Total drowsiness score during the first 4 hours after treatment (using the mean score as measured by the area under the curve

			and adjusted for the baseline drowsiness score)
Day 1 Unpleasant Taste (AUC)	c1taste_area		Cycle 1 Day 1 Total unpleasant taste score during the first 4 hours after treatment (using the mean score as measured by the area under the curve). Unpleasant taste score was not collected at baseline.
Day 1 Burning/Stinging Discomfort (AUC)	c1stinging_area		Cycle 1 Day 1 Total burning/stinging score during the first 4 hours after treatment (using the mean score as measured by the area under the curve). Burning/Stinging score was not collected at baseline.
120 mins: Did you take any other pain medications over the last hour?	c1v5_MEDUSED2	Yes, No	Cycle 1. Missing indicates the data was not collected
240 mins: Did you take any other pain medications over the last two hours?	c1v6_MEDUSED3	No, Yes	Cycle 1. Missing indicates the data was not collected
240 mins: Patient preference to continue mouthwash use.	c1v6_MOREDOSE	Yes, No	Cycle 1. Missing indicates the data was not collected
Baseline: Average Pain	c1v0_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.

5 mins: Average Pain	c1v1_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.
15 mins: Average Pain	c1v2_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.
30 mins: Average Pain	c1v3_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.
60 mins: Average Pain	c1v4_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.
120 mins: Average Pain	c1v5_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.
240 mins: Average Pain	c1v6_pain		Cycle 1. This is the average scores of mouth pain and throat pain where it was

			measured using 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible.
Day 1: Taste of the Oral Rinse	c2v1_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible
Day 2: Taste of the Oral Rinse	c2v2_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible
Day 3: Taste of the Oral Rinse	c2v3_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible There was a typo in the publication (eTable 1) for IQR of Doxepin, which should be corrected from (0-4.0) to (1-4.0)
Day 4: Taste of the Oral Rinse	c2v4_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible
Day 5: Taste of the Oral Rinse	c2v5_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible
Day 6: Taste of the Oral Rinse	c2v6_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible
Day 7: Taste of the Oral Rinse	c2v7_TASTE		Cycle 2. 0-10 scale, with 0=Acceptable and 10=Terrible
Day 1: Stinging/Burning	c2v1_STINGING		Cycle 2. 0-10 scale, with 0=No stinging or burning and 10=Worst stinging or burning possible There was a typo in the publication (eTable 1) for IQR of DLA, which should be corrected from (3.0) to

			(0-3.0)
Day 2: Stinging/Burning	c2v2_STINGING		Cycle 2. 0-10 scale, with 0=No stinging or burning and 10=Worst stinging or burning possible (eTable 1) for IQR of DLA, which should be corrected from (3.0) to (0-3.0)
Day 3: Stinging/Burning	c2v3_STINGING		Cycle 2. 0-10 scale, with 0=No stinging or burning and 10=Worst stinging or burning possible
Day 4: Stinging/Burning	c2v4_STINGING		Cycle 2. 0-10 scale, with 0=No stinging or burning and 10=Worst stinging or burning possible There was a typo in the publication (last paragraph of page 1487) for the following sentence: • day 4 (1.8 points [95% CI, 0.7-2.5 points], P = .002) The upper limit of 95% CI should be corrected from 2.5 to 2.9
Day 5: Stinging/Burning	c2v5_STINGING		Cycle 2. 0-10 scale, with 0=No stinging or burning and 10=Worst stinging or burning possible
Day 6:	c2v6_STINGING		Cycle 2. 0-10 scale,

Stinging/Burning			with 0=No stinging or burning and 10=Worst stinging or burning possible
Day 7: Stinging/Burning	c2v7_STINGING		Cycle 2. 0-10 scale, with 0=No stinging or burning and 10=Worst stinging or burning possible
Day 1: Mouth Pain Now	c2v1_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 2: Mouth Pain Now	c2v2_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 3: Mouth Pain Now	c2v3_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 4: Mouth Pain Now	c2v4_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 5: Mouth Pain Now	c2v5_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 6: Mouth Pain Now	c2v6_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 7: Mouth Pain Now	c2v7_MOUTHPAIN		Cycle 2. 0-10 scale, with 0=No pain and 10=Worst pain imaginable or possible
Day 1: Mouth/throat Pain Relief	c2v1_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was

			not collected
Day 2: Mouth/throat Pain Relief	c2v2_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was not collected
Day 3: Mouth/throat Pain Relief	c2v3_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was not collected
Day 4: Mouth/throat Pain Relief	c2v4_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was not collected
Day 5: Mouth/throat Pain Relief	c2v5_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was not collected
Day 6: Mouth/throat Pain Relief	c2v6_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was not collected
Day 7: Mouth/throat Pain Relief	c2v7_PAINRELIEF2	Yes, No	Cycle 2. Missing indicates the data was not collected
Maximum Total Pain Score reported within Cycle 1	c1_mx_pain		0-10 scale
Last Total Pain Score reported within Cycle 1	c1_last_pain		0-10 scale
Responders	responders	Yes (Reduction of 3.5 or more points), No (Reduction of less than 3.5 points)	
Change from Baseline to Maximum Pain	d_c1_v0_mxpain		c1v0_pain subtracted from c1_mx_pain
Change from Baseline to Last Pain	d_c1_v0_lastpain		c1v0_pain subtracted from c1_last_pain
Cycle 2 Study Rinse Used (Days)	c2_numdays_rinseused	2, 1, 6, 0, 3, 7, 5, 4	Missing indicates the patient did not participate in continuation phase
NSAID	nsaid	No, Yes	Baseline analgesic use during cycle 1.

Non-NSAID	nonnsaid	No, Yes	Baseline analgesic use during cycle 1.
Short-acting Opioid	saopioid	Yes, No	Baseline analgesic use during cycle 1.
Long-acting Opioid	laopioid	No, Yes	Baseline analgesic use during cycle 1.
Others	others	No, Yes	Other baseline analgesic use during cycle 1.
NSAID:Continuation	nsaidc	No, Yes	Baseline analgesic use during cycle 2. Patients that did not proceed to continuation phase were counted as No.
Non-NSAID:Continuation	nonnsaidc	No, Yes	Baseline analgesic use during cycle 2. Patients that did not proceed to continuation phase were counted as No.
Short-acting Opioid:Continuation	saopioidc	No, Yes	Baseline analgesic use during cycle 2. Patients that did not proceed to continuation phase were counted as No.
Long-acting Opioid:Continuation	laopioidc	No, Yes	Baseline analgesic use during cycle 2. Patients that did not proceed to continuation phase were counted as No.
Others:Continuation	othersc	No, Yes	Other baseline analgesic use during cycle 2. Patients that did not

			proceed to continuation phase were counted as No.