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Treatment of severe mucositis pain with oral ketamine mouthwash

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Abstract

Purpose—Mucositis is a significant complication of intensive chemotherapy or hematopoietic cell transplantation (HCT), with few treatment options. Ketamine mouthwashes have been used for pain relief, but supporting evidence is limited. The primary objective of this study was to assess the reduction in pain intensity of stomatodynia and odynophagia compared to baseline assessment.

Methods—This open-label, prospective, phase II interventional study (NCT01566448) was conducted from February 2012 through July 2015. Patients with grade 3 or 4 oral mucositis according to the World Health Organization (WHO) scale as a result of chemotherapy were treated with ketamine mouthwash 20 mg/5 mL four times daily and every 4 h as needed.

Results—Thirty patients were enrolled and a total of 136 assessments were conducted. A statistically significant reduction in pain scores of 2 and 3 points was achieved after 1 h and 3 days, respectively ($p < 0.0001$, $p = 0.0003$). Pain scores were significantly improved while swallowing, reduced 1 and 4 points at 1-h and 3-day assessment, respectively ($p = 0.0006$, $p = 0.0001$). No patients developed adverse effects related to ketamine administration.

Conclusion—Ketamine mouthwashes resulted in clinically meaningful and statistically significant reduction in pain scores, have an acceptable safety profile, and can be a useful adjunctive treatment in the multi-modal management of severe mucositis.

Keywords

Ketamine; Mouthwash; Oral; Mucositis; Pain; Transplant

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Compliance with ethical standards This study (ClinicalTrials.gov Identifier, NCT01566448) was approved by the Protocol Review Monitoring Committee at the West Virginia University (WVU) Cancer Institute and the Institutional Review Board at WVU Medicine.

Conflict of interest The authors declare that they have no conflict of interest.

Introduction

Mucositis has significant quality of life and clinical consequences for patients undergoing antineoplastic cytotoxic therapies. Oral mucositis occurs in approximately 40% of patients receiving standard dose chemotherapy, 80% of patients receiving radiation therapy to the head and neck, and up to 100% of patients undergoing a hematopoietic cell transplant (HCT) [1]. Mucositis and associated pain are consistently reported as extremely distressing for patients and may involve erythema, inflammation, bleeding, and ulceration. Pain from oral mucositis has been reported as one of the most debilitating side effect by patients receiving HCT. Mucositis also has the potential to impact the effectiveness of cancer treatment as it is a dose-limiting toxicity resulting in cessation or reduction of treatment in 35% of patients receiving chemotherapy [2–4].

As a result, many agents and strategies have been investigated to alleviate this pain, to prevent the incidence of mucositis, or to decrease the severity of mucositis. Unfortunately, few available options have proven useful. One marketed agent is a recombinant human keratinocyte growth factor, palifermin, and despite its approval to reduce the incidence and duration of oral mucositis, it has seen limited utility due to questionable clinical benefit and high acquisition costs. Current standard of care focuses on palliation and includes systemic opiate analgesics for moderate to severe mucositis pain, topical anesthetics and mucosal coating agents for moderate pain, and bland rinses for mild pain. Data supporting these management options are limited. Other agents that have been investigated with variable responses are oral capsaicin, oral sulfasalazine, and growth factor mouthwashes [5].

Ketamine is a sedative hypnotic with anesthetic and analgesic properties and with reported benefit when used topically. Ketamine works by selectively depressing the thalamoneocortical system, non-competitively blocking *N*-methyl-D-aspartate (NMDA) receptors, and having intrinsic sympathomimetic activity. Ketamine also appears to selectively interrupt association pathways in the brain producing somatesthetic sensory blockade. Ketamine is FDA approved for induction and maintenance of general anesthesia but has also been used for procedural sedation, refractory severe pain, and acute respiratory failure in children. Local administration of ketamine to the limbs of patients with complex regional pain syndrome has been shown to cause a reduction in allodynia in a double-blind placebo controlled study. Peripheral administration of ketamine was shown to have antinociceptive efficacy similar to that of systemic administration, likely mediated by NMDA antagonism [6]. Ketamine also has the modest anti-inflammatory properties which could be beneficial in mucositis pain relief.

Ketamine oral rinse was described in a case report of a 32-year-old female with radiation-induced mucositis pain refractory to compounded topical solutions (containing lidocaine, diphenhydramine, nystatin, and magnesium hydroxide/aluminum hydroxide), transdermal fentanyl, and intravenous hydromorphone. She experienced decreased stomatodynia and odynophagia and was able to decrease the dose of her systemic opiate analgesics [7]. A retrospective chart review of ketamine mouthwash in eight patients over a period of 4 years was conducted but the inconsistent reporting of pain scores was difficult to quantify. However, the authors noted that ketamine may provide a viable treatment option for

mucositis pain [8]. We prospectively evaluated ketamine as an oral mouthwash to provide pain relief for patients with severe oral mucositis.

Methods

Study objectives

The primary objective of this study was to assess the reduction in pain intensity of stomatodynia and odynophagia compared to baseline assessment as reported by the patient on a numeric scale. Secondary objectives include assessing patient-reported onset and duration of effect (as defined below), reduction in both narcotic analgesic use and topical lidocaine use, and improvement in patient-reported sleep quality, safety, and tolerability.

Patients

Patients eligible for inclusion were 18 years of age or older, received at least one dose of chemotherapy, had grade 3 or 4 oral mucositis according to the World Health Organization (WHO) oral mucositis scale [9], and signed the informed consent. Causative chemotherapy could include conditioning regimens for allograft, autograft, or chemotherapy alone. Patients were excluded if they had any documented hypersensitivity to ketamine; received prior ketamine doses by any route within 48 h of study initiation; were pregnant or breastfeeding; had schizophrenia, acute psychosis, or any psychiatric disorder that could be dangerous if exacerbated; or were unable to render informed consent. This study (ClinicalTrials.gov Identifier, NCT01566448) was approved by the Protocol Review Monitoring Committee at the West Virginia University (WVU) Cancer Institute and the Institutional Review Board at WVU Medicine.

Preparation

The solution was prepared by the pharmacy in batches of 24 individual oral syringes containing a 5-mL dose. A 5-mL vial of ketamine 100 mg/mL solution was diluted with normal saline to a final concentration of 20 mg/mL, drawn into unit-dose syringes, sealed with tamper-evident caps, and stored in automated dispensing cabinets on the patient's unit. Each syringe was given an expiration date of 7 days from preparation when stored at room temperature [10].

Study protocol

This was an open-label, prospective, phase II interventional study conducted at a single institution. Patients were treated with ketamine oral mouthwash 20 mg/5 mL swish and spit scheduled four times daily and additional doses permitted every 4 h as needed. Dosing was based on methods from prior published retrospective reports. [7, 8] Patients were asked to swish the solution for at least 30 s. Gargling the solution was allowed but patients were asked not to swallow the dose. All patients were permitted to continue analgesic therapy and topical lidocaine-based solutions, such as compounded admixtures with any combination of viscous lidocaine, diphenhydramine, nystatin, aluminum/magnesium antacids, and/or corticosteroids, often referred to as "Clark's solution" or "magic mouthwash" [11]. Topical lidocaine doses were recommended to be separated by at least 1 h from the ketamine rinse. Patients were also asked to refrain from eating or drinking for at least 30 min after each

ketamine dose. Patients were removed from the study on the day when their mucositis had resolved to less than grade 3. Removal from the study was also permitted by request from either the patient or physician or due to lack of efficacy, defined as no decrease in pain scores for three consecutive days.

Assessment

Baseline assessments were performed prior to initiating therapy with ketamine mouthwashes, 1 h after the first dose of ketamine and then daily thereafter for up to 7 days. Pain scores were assessed on a numeric scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain. Patients were asked to score pain at rest and when swallowing. Sleep quality was assessed on a 0 to 10 numeric scale, with 0 representing no sleep and 10 representing optimal sleep. Patients were assessed for food intake by the investigators, classified as none, liquids only, soft food only, or normal diet. Patients self-reported the onset and duration of effects categorically. Onset of effect was reported as either no effect, 0–15 min, 16–30 min, 31–45 min, 46–60 min, or greater than 1 h. Duration of effect was reported as either no effect, less than 1 h, 1–2 h, 2–3 h, 3–4 h, or 4 or more hours. The WHO oral mucositis severity grade was recorded daily.

Topical lidocaine-based solution usage was documented as the number of administrations per 24-h period. Narcotic analgesic use was reported as intravenous (IV) morphine equivalents over a 24-h period. All analgesics including oral, transdermal, intermittent IV, and PCA were converted to IV morphine equivalents based on a standard opioid equivalency table [12] (see Table 1). Baseline assessment of lidocaine use and morphine equivalents included the 24 h prior to the first dose of ketamine. Investigators assessed for adverse events, altered mental status, and recorded patient-reported outcomes (PRO) on data collection sheets with daily assessments of patient's alertness, communication responsiveness, and full orientation with their situation and surroundings. Wilcoxon's sum rank test was used in the data analysis on continuous variables and Fisher's exact test was used for categorical variables.

Results

Thirty patients were enrolled and a total of 136 unique assessments were conducted. Patients were on study for a median of 4 days (range 1–9) and received a median of 3.5 doses of ketamine per patient/day (range 1–5.7). The majority of patients had a diagnosis of acute myeloid leukemia (AML) and received myeloablative conditioning for an allogeneic transplant. The median grade of mucositis at baseline and on each study day was 3 with a range of 3–4. No patients in this study received palifermin. Baseline demographic details are described in Table 2.

A statistically significant decrease in pain scores was seen in the assessments performed both when resting and when swallowing at the 1-h assessment (reduction of 2 and 2.5 points, respectively, $p < 0.0001$ and $p = 0.0006$) and sustained at the day 3 assessment (reduction of 3 and 4 points, respectively, $p = 0.0003$ and $p = 0.0001$). Sleep quality was assessed as a surrogate marker for patient quality of life. Sleep quality significantly improved from a median rating of 5 to 6 ($p = 0.006$) after the first night and then sustained that improvement

through day 3 ($p = 0.034$). Concomitant lidocaine-based oral solutions were used by 90% ($n = 27$) of patients and were significantly reduced by a median of 1 dose per patient/day (range +3 to −4) ($p = 0.029$) after initiation of ketamine mouthwashes. The median daily requirement of IV morphine equivalents per patient appeared to be reduced by 22 mg (range +85.8 to −70.6 mg), but this did not reach statistical significance ($p = 0.145$). Patient outcomes are summarized in Table 3.

The onset of action was noted within 15 min of the dose in the majority of patients and reported to last for 1–3 h (Fig. 1). Tolerability of the solution was acceptable and several patients commented that the solution was preferable to the lidocaine-based solutions due to less burning and irritation. Twenty-nine of the 30 patients were removed from study due to resolution of their mucositis to less than grade 3. One patient (3%) was withdrawn from the study at the physician's discretion due to altered mental status, reported to be due to continuous intravenous narcotics and onset of sepsis and not deemed related to ketamine mouthwashes.

Discussion

Our study is the first prospective analysis of topical ketamine for the reduction of mucositis pain. We found a significant reduction in pain scores from baseline, as well as an improvement in sleep quality. Although pain is a subjective measure and varies greatly from patient to patient, applying a numeric scale to rate pain has been widely adopted as an acceptable way to quantify and track changes in intensity. Previous studies evaluating mucositis pain relief have cited a reduction in 2 points on a numeric 10-point scale to be "clinically" significant [13, 14]. While the assessment of generalized body pain has become routine in most institutions and is available in most charts for review, in order to accurately assess localized pain associated with oral mucositis and the relief of that pain by a specific intervention, a prospective evaluation of data was required.

Comparing outcomes from subsequent assessments to baseline (prior to ketamine) removed inter-patient variability of pain scores. The possibility of intervention bias (patients reporting lower pain scores as they are receiving treatment) was likely minimal, since no changes were made to the patients' current intensive systemic and local treatments at the time of ketamine intervention. Most of the patients were previously receiving topical lidocaine in the study and we did not inform patients that we would be recording the amount used in order to minimize patient request bias. One-hour assessment after initial dose was thought to be the most accurate predictor of the efficacy of ketamine mouthwashes, as the severity of mucositis will be most similar to baseline. As the time from baseline assessment increased, we acknowledge that there would be greater variation in the severity of their mucositis which may be reflected in the pain assessments.

We assessed the tolerability and palatability of the oral solution. For patients experiencing this degree of mucosal damage, formulations that cause additional discomfort are not ideal. All patients reported that the solution was tolerable, and in most cases, preferable to the lidocaine-based solutions. Some patients reported a metallic taste, but that it was not overly unpleasant. A few patients commented that the 5-mL volume was not enough quantity and

suggested a larger volume would be more beneficial. Absorption through mucosal membranes should be minimal, but with severe ulcerations, the true amount of systemic absorption is unknown. Ketamine is known to occasionally produce laryngospasm which could be problematic in a patient with mucositis, but no incidences of this occurred during the study. No patients were noted to have systemic toxicities, specifically psychogenic or dissociative effects, related to mucosal absorption of ketamine.

Given that our study did not find high rates of adverse effects, consideration could be given to the investigation of higher concentrations of ketamine or larger volumes in attempt to increase the topical efficacy. In future investigations, although patients had clinical assessments performed as part of their standard of care, detailed assessments for ketamine-specific adverse effects would be beneficial, as the authors acknowledge that patient-reported outcomes may be subject to ketamine-induced amnesia. Other modifications that may warrant investigation would be substituting the normal saline diluent for a more viscous substance to allow for mucosal adhesion or potentially adding flavoring for palatability. Additional studies evaluating ketamine and lidocaine on an alternating schedule or possibly in a combination product may also show additional pain relief. A recent large phase III randomized study found that a doxepin rinse was effective at reducing pain scores by a mean of 2 (on a 10-point scale) which is synonymous with the results we report in this study with ketamine rinses; an evaluation directly comparing the two or the combination of both may give further information to help manage the pain of oral mucositis.

Conclusion

In our study, oral ketamine mouthwash use resulted in a clinically meaningful and statistically significant reduction in pain scores for stomatodynia and odynophagia, improved sleep quality, and reduced oral lidocaine utilization for patients with severe oral mucositis. There was no apparent toxicity, oral tolerability was favorable, and cost was minimal. Ketamine mouthwash could provide a useful adjunctive treatment in the multi-modal management of severe oral mucositis associated with chemotherapy.

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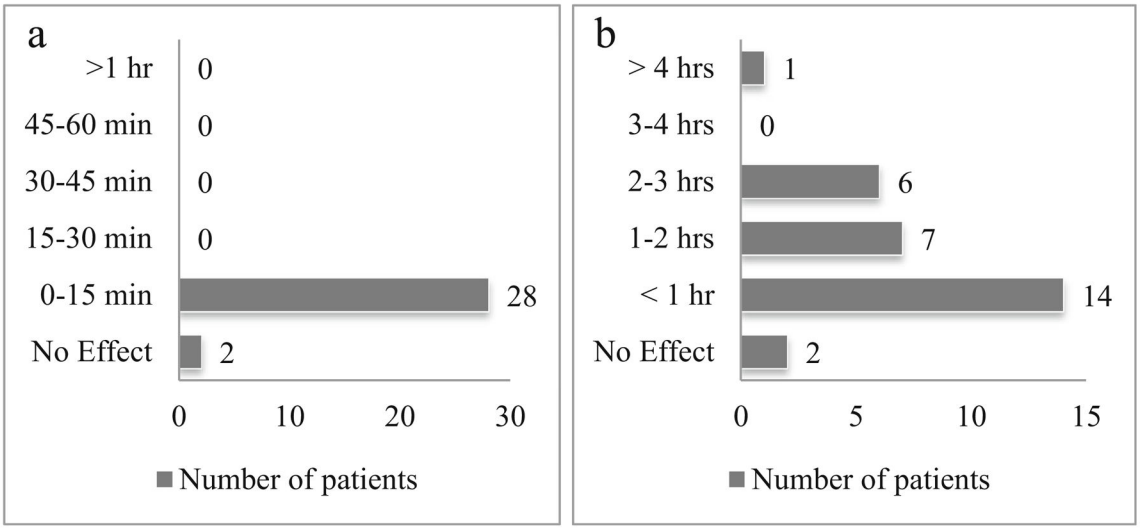

Fig. 1.

a Onset of effect from ketamine mouthwashes. **b** Duration of effect of ketamine mouthwashes

Table 1

Opioid equivalency table

Drug	Dose (mg) parenteral	Dose (mg) oral
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone		20
Methadone	5	5
Codeine	120	200
Hydrocodone		30
Meperidine	75	300
Fentanyl	0.1	

Table 2

Demographics

Number of patients	***N* = 30**	**(%)**
Median age in years (range)	44	(23–67)
Gender		
Female	17	(57)
Male	13	(43)
WHO mucositis grade at enrollment		
Grade 3	16	(53)
Grade 4	14	(47)
Primary malignancy		
AML	17	(57)
Lymphoma	6	(20)
CML	2	(7)
ALL	2	(7)
Other	3	(10)
llogeneic conditioning	23	(77)
Autologous conditioning (CBV)	2	(7)
Other	5	(16)
Allogeneic conditioning regimen:	*N* = 23	
Flu/Bu4	12	(52)
Bu/Cy	5	(22)
Flu/Bu4/TBI	3	(13)
Cy/TBI	2	(9)
Flu/Cy/TBI	1	(4)
Parenteral nutrition	8	(27)

AML acute myeloid leukemia, *CML* chronic myeloid leukemia, *ALL* acute lymphoid leukemia, *CBV* cyclophosphamide/carmustine/etoposide, *Flu/Bu4* fludarabine/busulfan, *Bu/Cy* busulfan/cyclophosphamide, *Flu/Bu4/TBI* fludarabine/busulfan/total body irradiation, *Cy/TBI* cyclophosphamide/total body irradiation, *Flu/Cy/TBI* fludarabine/cyclophosphamide/total body irradiation

Table 3

Endpoints

Objective	Baseline	1-h post		Day 1		Day 2		Day 3	
	Median (range)	Median (range)	*p* value	Median (range)	*p* value	Median (range)	*p* value	Median (range)	*p* value
Pain score at rest	6 (1–10)	4 (0–10)	<0.0001	5 (0–10)	0.005	3 (0–9)	0.0001	3 (0–8)	0.0003
Pain score when swallowing	9 (2–10)	6 (0–10)	0.0006	8 (1–10)	0.014	5 (0–10)	0.0001	4 (0–10)	0.0001
Sleep quality	5 (0–10)	n/a	n/a	6 (1–10)	0.006	6.5 (0–9)	0.019	6 (2–10)	0.034
IV morphine equivalents mg/24 h/pt	46 (0–242)	n/a	n/a	34 (0–202)	0.37	26 (1–230)	0.5	24 (0–173)	0.145
Lidocaine usages/day/patient	3 (0–5)	n/a	n/a	2 (0–8)	0.093	2 (0–5)	0.045	1 (0–4)	0.029

n/a not applicable