Ketamine Mouthwash versus Placebo in the Treatment of Severe Oral Mucositis Pain in Children with Cancer: A Randomized Double-Blind Placebo-Controlled Trial

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Abstract

Background and aims: Oral mucositis (OM) is common and distressing toxicity in children on chemotherapy. There is limited number of safe and effective therapeutic options available for OM. Ketamine oral rinse has shown promising results in few studies in adults. This randomized, double-blind placebo-controlled trial aimed to test the efficacy of ketamine mouthwash in reducing chemotherapy-induced severe OM pain in children. Methods: Children aged 8-18 years with severe OM were randomized to a single dose of ketamine mouthwash (4 mg/ml solution; dose 1 mg/kg) or a placebo. A sample size of 44 patients was determined. Pain score (6-point faces scale) was noted at baseline and 15, 30, 45, 60, 120, 180, and 240 min. The outcome variables were a reduction in pain score, need for rescue medications, and adverse events. Results: The baseline characteristics were comparable in the two groups. The mean OM pain at 60 min decreased by 1.64 points (CI 1.13-2.14) in the ketamine group and 1.32 points (CI 0.76-1.87) in the placebo group (p=0.425), with a group difference of 0.32 points. Rescue pain medication (at 60 min) was required in 13.6% in the ketamine group and 18.2% in the placebo group (p=1.000). There were no significant adverse events observed. Conclusions: Among children on cancer chemotherapy with severe OM, ketamine mouthwash at a dose of 1 mg/kg did not significantly reduce OM pain. It did not decrease the need for rescue pain medications. Further research is warranted to test higher doses of ketamine for a clinically significant effect.

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Conclusions: Among children on cancer chemotherapy with severe OM, ketamine mouthwash at a dose of 1 mg/kg did not significantly reduce OM pain. It did not decrease the need for rescue pain medications. Further research is warranted to test higher doses of ketamine for a clinically significant effect.

INTRODUCTION

Oral mucositis (OM) refers to the inflammation and ulceration of the oral cavity's mucous membranes. It is a common adverse effect of cancer treatment, including both chemotherapy and radiotherapy. Children are more prone to the development of OM following cancer chemotherapy as compared to adults. The reported incidence rates range from 50-80% in children receiving cancer chemotherapy and 90-100% during a hematopoietic stem cell transplant.[1,2,3] However, OM in children has also been reported to heal faster in comparison to that in adults.[4] The OM following chemotherapy often develops within a week of starting chemotherapy, and usually resolves by the end of 2nd week. The OM leads to a significant decline in the quality of patient's life, which stems from the considerable pain at rest and a burning feeling in the oral cavity (stomatodynia) as well as on swallowing (odynophagia), difficulty in swallowing (dysphagia) and difficulty in speaking (dysarthria). This leads to inadequate oral intake causing poor nutrition and weight loss and a possible requirement of parenteral nutrition. It also predisposes to secondary infection of the oral lesion, in addition to prolonging the duration of the hospital course and increasing the cost of treatment. It may entail a dose reduction or discontinuation of a chemotherapeutic agent, which would naturally correlate with a poorer prognosis for the primary malignancy. Currently, the mainstay of therapy for OM is pain management, comprising of systemic (oral, parenteral) and topical agents. Several agents have been tried for the prevention and treatment of OM, with a handful showing a beneficial role, such as palifermin, low-level laser therapy, and doxepin oral rinse.[5,6,7]Other interventions with possible efficacy include oral hygiene protocols and cryotherapy. There is a paucity of evidence-based recommendations for OM pain in children with cancer.

Ketamine is a dissociative anesthetic agent with a potent NMDA receptor-channel blocking activity. It has also been shown to have some opioid-like effects and anti-inflammatory properties.[8]Commonly seen adverse effects of ketamine include sedation, nausea, vomiting, hallucinations, excessive salivation, and ataxia.[9,10] However, these effects have been reported to be minimal with its topical use. Ketamine has been used for pain relief in many conditions, including cancer-related pain. Topical ketamine has also been found to be a safe and effective analgesic for decreasing post-tonsillectomy pain in children.[11,12]Ketamine oral rinse has shown promising results in a few non-randomized studies in adults with chemotherapy-related OM pain.[13,14,15] This randomized, double-blind placebo-controlled trial aimed to test the efficacy of ketamine mouthwash in the reduction of chemotherapy-induced severe OM (WHO grade-III or grade-IV) pain.

MATERIALS AND METHODS

2.1 Study design and patients

This study was conducted from October 2018 to February 2020 over 17 months at the Department of Pediatrics and Department of Medical Oncology in All India Institute of Medical Sciences (AIIMS), New Delhi, India. The Institute Ethics Committee approved the study protocol (IECPG-328/18.07.2018, RT-1/2018). The trial was registered in the Clinical Trial Registry of India [Trial registration number CTRI/2018/08/015499].

Patients were eligible for enrolment if they were between 8 to 18 years of age, received at least one cycle of cancer chemotherapy and had severe OM (grade-III or grade-IV by WHO oral mucositis grading scale) with an OM pain score of 2 or more (on a 6-point Wong-Baker faces pain rating scale[16], with 0 being no pain and 5 being maximum pain). The exclusion criteria included intake of a systemic analgesic within 4 hours or topical analgesic to the oral cavity within one hour before randomization, administration of ketamine by any route within 48 hours of randomization, and any contra-indications to the use of ketamine (documented hypersensitivity, raised intracranial pressure, hypertension). In all the cases, written informed consent was taken from parent/ legally authorized representative (LAR).

2.2 Definitions

WHO Oral Mucositis grading scale

Grade-0- None

Grade-I: Oral soreness, erythema

Grade-II: Oral erythema, ulcers, solid diet tolerated

Grade-III: Oral ulcers, liquid diet only

Grade-IV: Oral alimentation impossible

Intensity of chemotherapy

The intensity of chemotherapy was classified into four levels according to the expected duration of severe neutropenia:

1. Minimally myelosuppressive chemotherapy: Not expected to induce severe neutropenia [e.g., maintenance therapy in acute lymphoblastic leukemia (ALL), chemotherapy for Hodgkin lymphoma]
2. Briefly myelosuppressive chemotherapy: Expected duration of severe neutropenia [?]10 days (e.g., induction, consolidation, interim maintenance, delayed intensification therapy of standard-risk ALL)
3. Strongly myelosuppressive chemotherapy: With the expected duration of severe neutropenia >10 days (e.g., chemotherapy for acute myeloid leukemia (AML), and induction, consolidation, interim maintenance, delayed intensification therapy of high-risk ALL)
4. Myeloablative chemotherapy: Requiring hematopoietic stem cell transplantation (HSCT) to reconstitute bone marrow function (e.g., Post HSCT)

2.3 Randomization

The study was designed as a randomized, double-blind, parallel-group controlled trial. The eligible children were randomized into two groups after enrolment into the study: Intervention (I) and control (C) group. Computer-generated block randomization with variable block sizes was employed. The person responsible for the preparation and labelling of study drug vials was not involved in enrolling the subjects, administering the intervention, or analyzing the data. Each enrolled patient was administered the drug from the next serially labelled vial, corresponding to the sequence of his/her enrolment. The ketamine and placebo mouthwash preparations were identical in appearance, taste, and smell. The labelling on the drug vial mentioned only the serial number, and the serial number's randomization sequence was not revealed to the principal investigator. Thus, both the patient and the principal investigator were masked to the assigned group. After the completion of enrolment, the analyst was provided with the randomization list mentioning groups "A" and "B" without revealing the actual ketamine and placebo groups. The statistical analysis was hence done without the knowledge of the study arms (triple-blind). The actual study arms were disclosed after all enrolment and statistical analyses were completed. Allocation concealment was ensured by randomization of the patients coupled with using identical intervention and control vials.

2.4 Intervention and assessment

All enrolled children were first administered supervised mouthwash with 5 ml drinking water, as oral swish for 30 seconds followed by spitting and without swallowing. This exercise was carried out to assess the adequacy of the mouthwash technique by the patient. Those children who were not able to follow commands or not able to carry out the mouthwash procedure adequately were planned not to be administered the mouthwash, and not to be included for analysis. However, all the enrolled children were able to follow the instructions adequately.

Children randomized to the intervention group received ketamine mouthwash (prepared as 4 mg of ketamine in 1 ml solution by diluting marketed formulation of ketamine in an appropriate pharmaceutical diluent) at a dose of 0.25 ml/kg body weight mouthwash solution (i.e., ketamine 1 mg/kg body weight), with the maximum dose set as 40 mg ketamine, i.e., 10 ml mouthwash solution. The children in the control group received placebo mouthwash (containing the same diluent that was used to prepare the ketamine mouthwash

solution), at a dose of 0.25 ml/ kg body weight, with maximum dose set as 10 ml. The mouthwash was administered in a supervised manner as an oral swish for 30 seconds, followed by spit. In the case of the patient swallowing the solution accidentally, he/she was planned to be closely monitored for vitals and any adverse effects of ketamine.

Based on a study by Bredlau et al[17], oral ketamine doses ranging from 0.25–1.5 mg/kg/dose three times a day for two weeks was found to be safe in children. Hence, the intervention dose in this study, even if accidentally swallowed, was to be considered safe, with the requirement of only close monitoring for 4 hours. But such a patient was decided not to be considered for analysis, because of a possible effect of systemic absorption of ketamine on OM pain. However, none of the enrolled children swallowed the mouthwash solution.

A 6-point Wong-Baker faces pain rating scale (0-5) was used for assessing oral mucositis pain. The patients were assessed for OM pain score and adverse events at baseline, every 15 minutes in the first hour, and hourly thereafter for the next 3 hours (total 4 hours).

The patients were instructed not to take any analgesic medication until one hour after the mouthwash administration. The patients were assessed for pain score, and if required, oral paracetamol (intravenous in case of inability to take the oral drug) was given at a dose of 15 mg/kg. If the patient still complained of pain one hour after administration of paracetamol, oral tramadol (IV in case of inability to take the oral drug) was planned to be administered at a dose of 1 mg/kg/dose (maximum 40 mg). If the patient complained of intolerable pain within the first hour of administration of the mouthwash, the patient was planned to be given analgesics as described above, with no further monitoring as per the study protocol and exclusion from analysis. However, no patient required rescue analgesic medication before completion of 60 minutes.

Outcome assessment

The primary objective of the study was to determine the mean reduction of OM pain (on a numeric of a 6-point scale) in children on cancer chemotherapy at 1-hour after administration of ketamine mouthwash, as compared to placebo. Secondary outcomes included a reduction in the requirement of other topical and systemic analgesics and the determination of adverse events associated with the use of ketamine mouthwash.

2.6 Sample Size

Based on the study by Shillingburg et al[13]**,**assuming a mean pain score reduction of 3-points in the intervention group and 2-points in control, with a standard deviation (SD) of 1, level of confidence 95%, and power 90%, a sample size of 44 patients (22 in each arm) was determined and targeted for accrual, based on the two-sample t-test with an equal-variance assumption. Because of the short follow-up period (4-hour), no additional patients were targeted for enrolment.

2.7 Statistical analysis

Statistical analysis was done using Stata 14.2 (Stata Corp, College Station, TX). The categorical variables were tested for significance using Fisher's exact test, and the continuous variables, including primary outcome, were tested for significance using the two-sample t-test. The p-value was based on two-sided comparisons. There were no protocol violations, and the intention to treat analysis was employed. The analyst was masked to the groups (ketamine, placebo).

RESULTS

A total of 64 patients were screened for enrollment during the study period of 17 months at the two centers in a tertiary healthcare institute. A total of 44 patients, including both inpatient and outpatient, were enrolled in the study. The study flow chart is shown in Figure 1. The baseline characteristics were all well-balanced between the two arms (Table 1).

3.1 Primary outcome

The mean OM pain score reduction at 60 min after drug administration in the ketamine group was 1.64 points (on the 6-point faces pain rating scale), while that in the placebo group was 1.32 points, with a

group difference of 0.32 points. The difference in the pain score between the two groups was not statistically significant (p=0.425). (Table 2)

The reduction in OM pain score in the two groups was measured at 15, 30, 45, 60, 120, 180, and 240 minutes after drug administration. The maximum difference in the mean reduction in pain score between the two groups was noted at 45 minutes (0.36 points) (Figure 2).

3.2 Secondary outcomes

3.2.1 Reduction in the requirement of analgesics

In the ketamine group, three out of 22 children (13.6%) required rescue medication for pain relief at 60 minutes after administering ketamine mouthwash. This included two children requiring topical lignocaine and one requiring oral paracetamol. In the placebo group, four out of 22 children (18.2%) required the rescue analgesic medication: two required topical lignocaine and two required oral paracetamol. The difference in the requirement of analgesic rescue medication between the two groups was not statistically significant (p=1.000) (Table 2).

3.2.2 Toxicities

In the ketamine group, two children (9.1%) complained of adverse events. This included one child with vomiting and another child who complained of vertigo. In the placebo group, five children (22.7%) had an adverse event, including three children with vomiting, one with nausea, and one with pain in the abdomen. All the adverse events noted in the two groups were transient and mild. The difference between the occurrence rates of adverse events in the two groups was not statistically significant (p=0.412) (Table 2).

DISCUSSION

This study demonstrated no significant efficacy of ketamine mouthwash (at a dose of 1 mg/kg) for OM pain reduction in children, both in terms of clinical significance (but there was an extra pain reduction of 0.32 points on a 6-point scale as compared to placebo) as well as statistical significance (p=0.425). A similar inference was suggested from the observation that there was no significant reduction in the requirement of rescue analgesic medications in the ketamine group as compared to placebo in the study. Ketamine mouthwash at 1mg/kg was safe, with only two children experiencing adverse events, both of which were mild and transient.

All the studies of ketamine mouthwash in severe oral mucositis pain in cancer patients have been provided in Table 3. There are noticeable differences in the patient profile and the study design in the previous studies as compared to the current study. A pain reduction of 1.64 points on the 6-point scale in the current study was comparable to the pain reduction of 2 points on a 10-point scale at 1-hour of drug administration in the study carried out by Shillingburg A et al[13], but it carries little significance as the placebo arm also demonstrating a pain reduction of 1.32 points on the 6-point scale in the current study.

There can be several possible reasons for the lack of significant pain reduction in the current study: (1) the most straightforward explanation is that ketamine mouthwash is truly ineffective for OM pain, as was statistically demonstrated by the current study. The underlying reason for this could be pharmacodynamic, in the sense that the local receptors in oral mucosa for ketamine action may not be adequate in number or function. However, ketamine gargles have been shown to significantly reduce postoperative sore throat, suggesting that there are indeed receptors for ketamine action in the oral mucosa.[18]The effect of mucosal inflammation and ulceration on such receptors is not precisely known, especially in children, and requires further research. (2) Another possible explanation could be that the dose of ketamine used in the study, i.e., 1 mg/kg (maximum 40 mg), was inadequate. Determining an appropriate dose for the study was difficult considering that all previous studies on ketamine mouthwash for OM was done in adults (all of which used a dose of 20 mg/dose of ketamine mouthwash). An arbitrary dose of 1 mg/kg/dose was chosen for this study. This dose was tried on three children with severe OM before starting the study; all three children reported some pain relief. However, considering the lack of efficacy of ketamine shown by this study, it might be

imperative to test a higher dose of ketamine mouthwash for OM before its benefit can be conclusively ruled out. (3) The third possibility is remote that the enrolled children were not able to appropriately understand and express their pain scores since the enrolled children were relatively older (8-18 years), and the pain scale used was a commonly employed and validated scale for children. (4) Similarly, periodic assessment of the drug formulation was done and drug adequately stored, thus eliminating the likelihood of the drug formulation being ineffective.

A major strength of this study was the design of a randomized, placebo-controlled trial. The masking and allocation concealment were ensured stringently in the study. A validated pain scale was used, which could be easily comprehended by the children. Supervised administration of the drug was done. There were no protocol violations and intention to treat analysis in the study.*Limitation:* This was a single-institute study (two centers). Although the enrolled children exhibited a variety of cancer profiles, the racial profile was similar for all children. The study required the administration of only a single dose ketamine mouthwash with a short follow up period. This was done keeping in mind that this was the first documented instance of the use of ketamine mouthwash in children with cancer, and the safety profile of the drug over long term use was not definitively known. The primary outcome for our study was decided as a reduction in pain score and not the reduction in the use of systemic analgesics, even though the underlying premise for the study was arguable to find a safe topical agent so that the adverse effects of the systemic analgesic drugs could be minimized. However, the overall requirement of systemic analgesics was less, as seen in the study's placebo arm, and it was much more challenging to demonstrate a statistical significance.

In conclusion, ketamine mouthwash at a dose of 1 mg/kg did not significantly reduce chemotherapy-induced severe oral mucositis pain in children, and it did not decrease the need for rescue pain medication. Further research is needed with a higher dose of ketamine before a definite conclusion can be drawn regarding the efficacy of ketamine mouthwash in children with oral mucositis pain in children with cancer.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Figure legends

Figure 1 : Study flow chart

Figure 2 : Reduction in oral mucositis pain score at different points of time after drug administration

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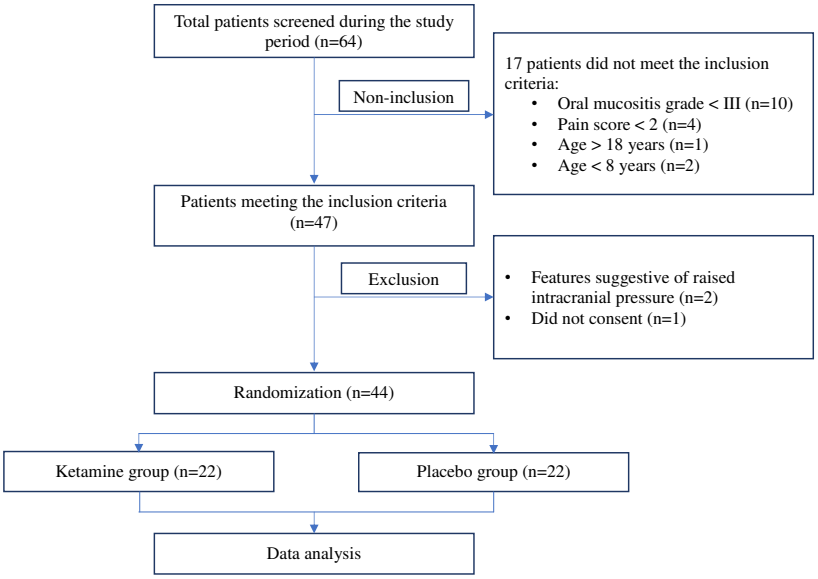

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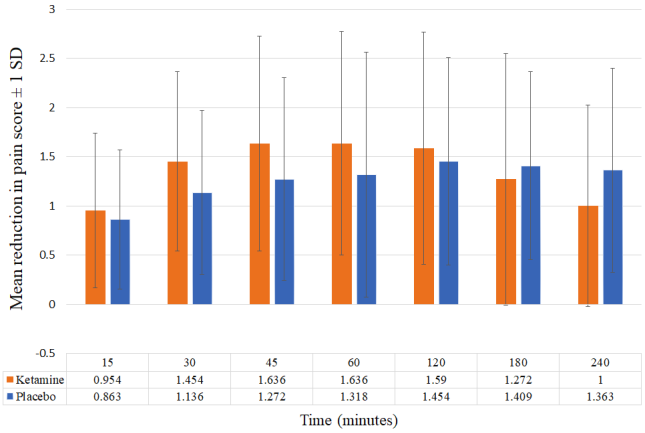

	15	30	45	60	120	180	240
Ketamine	0.954	1.454	1.636	1.636	1.59	1.272	1
Placebo	0.863	1.136	1.272	1.318	1.454	1.409	1.363

Figure 2: Reduction in oral mucositis pain score at different points of time after drug administration