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Oral cryotherapy: Too cool way for prevention of oral mucositis for concurrent chemo-radiotherapy.

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Abstract
Aim: To determine tolerability and effectiveness of oral cryotherapy on oral mucositis.
Settings and Design: Using an experimental study design, 30 patients were included in the study who received cisplatin with radiation at Tata memorial hospital.
Methods and Material: Participants received oral cryotherapy during concurrent chemo-radiotherapy. During cisplatin administration, oral cryotherapy was given for 5mins before, during, 5mins after and for radiotherapy it was given for 5mins before and 5mins after. Participants were assessed for cold tolerance using Visual Analogue Scale after receiving oral cryotherapy. They were followed up at the end of all 4 weeks for assessment of oral mucositis using Radiation therapy oncology group mucositis scale and pain score using Visual analogue scale.
Statistical analysis used: Results were displayed as mean ± standard deviation or frequency and percentage. Non-parametric Friedman test and Post-hoc Wilcoxon signed-rank test were also performed.
Results: Tolerability during radiotherapy scores was significant ($P < 0.05$). Using Radiation Therapy Oncology Group grading for oral mucositis and pain scores were compared over four weeks. The Friedman test was significant ($P < 0.001$) for both. Also, using Wilcoxon signed ranks tests ($P < 0.01$) revealed that week 2, week 3, and week 4 was significant in the reduction of oral mucositis. While for pain, it revealed that week 3 and week 4 reduces pain scores.
Conclusions: The tolerability of oral cryotherapy is found to be significant in radiation and also significant in reducing incidence of oral mucositis and pain score.

Key-words: *Cisplatin, oral mucositis, oral cryotherapy, radiation, tolerability*

Key Messages:

- *Cryotherapy is easily administered, bearable, and lack of adverse effects. Oral cryotherapy is suggested in preventing and reducing the severity of OM.*
- *Oral cryotherapy is a readily applicable and cost-effective prophylaxis can be recommended for preventing OM among cancer subjects receiving radiotherapy.*

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I. Introduction:

Oral mucositis (OM) is the most common cause of cancer therapies due to multicycle chemotherapy and radiotherapy with or without concurrent chemotherapy of head and neck cancer.[1] Cytotoxic radiotherapy and chemotherapy or both are becoming increasingly effective for treating malignancies but they are associated with both long- and short-term side effects.[2] Oral mucositis is one of the most recurrent and potentially severe complications of chemoradiotherapy which has a significant impact on a patient's quality of life. Mucositis is one of the chief limiting factors of chemoradiation for advanced head and neck carcinoma. While the management of other chemoradiotherapy related toxicities has improved, but the incidence of mucositis is still increasing.[3]

Oral mucositis presents as erythema and ulceration of the oral mucosa. Besides, the pharyngeal, laryngeal, and esophageal mucosa are also at danger for mucositis, especially in cancer patients undergoing Head & Neck RT. It is typically very painful, requiring opioid analgesics, and impairs nutritional intake and quality of life.[4-5] In Tata Memorial Hospital 77% of the patients treated with concurrent chemoradiotherapy in the postoperative setting, on the Radiation Therapy Oncology Group (RTOG) 9501 protocol, experienced > grade 3 acute toxicity. Even in the setting of definitive chemoradiation, toxicity is excessive, with 85% of patients experiencing Grade 3-5 toxicities, specifically, 43% of patients experience Grade 3-5 mucositis. Treatment delays and dosage adjustments can also occur resulting in dose reductions in subsequent cycles of chemotherapy and radiotherapy or even discontinuation of treatment. Dose reductions have been seen in 60% of patients and discontinuation of regimens in about 30%. Severe mucositis can entail a reduction in the chemotherapy dose or a treatment break in RT.[6-7]

The rapid progress in the understanding of oral mucositis creates a need for improved patient quality of life and the addition of prophylactic measures. As nurses working in oncology set up play an important role in the patient's outcome related to oral mucositis. Nurses are in prime position to understand, assess patient's oral status, and take measures to prevent oral mucositis. It is a prime responsibility as health care professionals to decrease the incidence or severity of mucositis as much as manageable. Nurses can positively influence patients by incorporating the evidence-based practice for the prevention of oral mucositis thereby improving the quality of life as well as the treatment outcome.

Several methods have been suggested for preventing chemotherapy-induced oral complications.[8-10] The amendment of the Multinational Association of Supportive Care in Cancer, 2007 (MASCC) guidelines has suggestions for oral mucositis in consideration of an intervention (i.e., strong evidence supports effectiveness in the treatment setting). The panel recommends that 30 minutes of oral cryotherapy be used to prevent oral mucositis in patients receiving bolus 5-Fluorouracil chemotherapy.[11] Besides, there have been several reports of reduced chemotherapy-induced OM by oral cryotherapy.[12-20] Oral cryotherapy is the application of ice chips or ice-cold water to the mouth. Oral cryotherapy for chemotherapy-induced OM requires that patients suck on ice chips before, during, and after infusions of cytotoxic drugs.[21] The rationale underlying oral cryotherapy is that ice can clench the blood vessels of the oral cavity membranes, therefore declining the vulnerability of the oral mucosa to mucotoxic agents. It is a low cost, natural treatment without serious side effects. An effective way for the prevention or treatment of oral mucositis has not been regulated and varies markedly among institutions. An increased emphasis on improved oral status begins with prophylactic measures. Oral cryotherapy (ice chips), the therapeutic administration of cold, is a preventive measure for oral irritation.

Based on these facts we undertook this study in order to verify the tolerability and efficacy of oral cryotherapy in preventing and alleviating chemo-radiotherapy induced oral mucositis and encourage its use in patients receiving concurrent chemo-radiotherapy protocol for head and neck carcinoma. The high prevalence of oral mucositis reported by patients undergoing concurrent chemoradiotherapy encourages studies aimed at evaluating ways to reduce a side effect with a great impact on patients' quality of life.

Aim: The aim of this study was to determine the tolerability and the effectiveness of oral cryotherapy on oral mucositis among patients receiving cisplatin with radiation.

Primary Objective:

- To assess ease and tolerability of oral cryotherapy.

Secondary Objectives:

- To find the incidence of oral mucositis among patients receiving concurrent chemo-radiotherapy after the administration of oral cryotherapy.
- To evaluate the effectiveness of oral cryotherapy on oral mucositis.

II. Subjects and Methods:

Sample and settings

Patients included in this study received cisplatin with radiation for head and neck cancer at the general and private day care and radiation therapy OPD's of Tata Memorial Hospital. Patients were followed up and evaluated daily at the Radiation treatment OPD (5days/week) and Day Care centers (once weekly or once 3 weekly) for 4 consecutive weeks after receiving concurrent chemo-radiotherapy. 30 patients with stage III or IV, non-metastatic squamous cell or undifferentiated carcinoma of the head and neck region, originating in the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx and unknown primary, with cervical lymphadenopathy were included in the study. These patients received radiation therapy to a dose of 66-70Gy/35# (definitive) or 60-66Gy/30-33# (adjuvant) along with concurrent chemotherapy cisplatin 40mg/m^2 weekly or 100mg/m^2 3 weekly. All patients were informed that they will receive Oral cryotherapy (Ice chips) that will be placed inside the mouth, while receiving concurrent chemo-radiotherapy in order to decrease the uptake of the drug by their oral mucosa and alleviate the pain they would experience in their mouth with the progress of therapy.

Instruments

1- Visual Analogue Scale (VAS) for cold tolerance

Ranks	**VAS index (1-9)**
0	1- Not tolerable
1	2 to 4 - Can tolerate
2	5 – Neutral
3	6 to 9 - No effect

2- Radiation Therapy Oncology Group (RTOG) scale for oral mucositis

GRADE	0 (None)	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life threatening)
	No changes over baseline	Irritation, may experience slight pain, not requiring analgesic	Patchy mucositis that may produce inflammatory serosanguinitis discharge, may experience moderate pain requiring analgesia	Confluent, fibrinous mucositis, may include severe pain requiring narcotic	Ulceration, hemorrhage, or necrosis.

3- Visual Analogue Scale (VAS) for pain assessment

Points	**VAS Index (0-10)**
0	No pain
1-3	Mild pain
4-6	Moderate pain
7-10	Severe pain

Procedure

Cryotherapy refers to the ice chips that were prepared in a manner that did not cause irritation in the mouth of the patients and that could be easily moved to every corner of the mouth. It was in semi-circular shape and measured about 1 inch in diameter and ½ inch width. Patients were instructed to swish the ice chips around their oral cavities starting 5mins before (T-5mins), during (T=30mins) and 5mins after (T+5mins) the administration of Cisplatin. Patients were instructed to swish the ice chips around their oral cavities starting before (T-5mins) and 5mins after (T+5mins) radiation therapy. Once the ice melts, patients were instructed to rinse the mouth with the liquid of melted ice to cool the large surface as possible of the oral mucosa and then they can swallow or spit out the water from the melted ice chips. Patients who experienced any pain or discomfort during the cryotherapy application were advised to continue after a maximum of 60secs break. Food or drinks were allowed to be consumed either before or after the session. If it was intolerable for the participants to continue the application then the intervention was stopped immediately.

Patients were assessed for cold tolerance using Visual Analogue Scale (VAS) each time during the administration of oral cryotherapy. Patients were also followed up weekly i.e. at the end of week 1, week 2, week 3 and week 4 for the assessment of oral mucositis using Radiation Therapy Oncology Group (RTOG) mucositis grading scale and effectiveness of oral cryotherapy in terms of pain score and use of pain medication using Visual Analogue Scale (VAS) for pain.

III. Data Analysis

Data was analysed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Subject demographics and baseline characteristics was summarized and outcome was measured in descriptive statistics (n, mean, standard deviation, and median, minimum, maximum). Categorical variables were summarized with counts and percentage. The Shapiro-Wilk test was used to check normality of each variable.

Primary endpoint analysis -

Primary endpoint is tolerability oral cryotherapy was measured using VAS for cold tolerance.

Descriptive statistics was used to summarize tolerability results for each time points (week 1, week 2, week 3 and week 4). If the variables were not normally distributed, a non-parametric Friedman test was carried out to test the difference between related samples i.e., Baseline till post 4 weeks. Post-hoc Wilcoxon signed-rank test was performed with Bonferroni correction of alpha for pair-wise comparison of mean rank difference between baseline week 1 and post week 4 of the treatment by each of the parameters.

Secondary end point analysis:

The secondary objective of the study is incidence of patients with oral mucositis after receiving oral cryotherapy and endpoint of this study is the percentage of patients with none, mild, moderate and severe grade oral mucositis was reported in frequency and percentage with 95% confidence interval for each time points (week 1, week 2, week 3 and week 4). P-trend test was used to compare change over the time in incidence of OM.

Efficacy analyses will be done for intent-to-treat (ITT) population and per protocol population (PP). Efficacy analyses will be analyzed using descriptive statistics.

Use of pain medications was analyzed descriptively and VAS for pain assessment was used which is a self-report measure using 11-point numeric scale.

All participants were assessed for pain at the end of each week (1st week, 2nd week, 3rd week and 4th week). If the variables were not normally distributed, a non-parametric Friedman test will be carried out to test the difference between related samples i.e., Baseline till post 4 weeks. Post-hoc Wilcoxon signed-rank test will be performed with Bonferroni correction of alpha for pair-wise comparison of mean rank difference between baseline week 1 and post week 4 of the treatment by each of the parameters.

Ethics

Institutional approval was received before the beginning of the study. All patients were informed about the procedure and their written consent obtained. All patients consented to participate in the study.

IV. Results:

Patient Characteristics

Baseline patient characteristics are presented in Table 1.

Table 1. Distribution of subjects according to demographic data

Characteristics		Frequency	Percent
Age (Mean ± SD)		50.97±11.55	
Gender	Male	30	100.0
Habits	No	7	23.3
	Yes	23	76.7
Smoking	No	25	83.3
	Yes	5	16.7
Tobacco chewing	No	11	36.7
	Yes	19	63.3
Alcohol	No	20	66.7
	Yes	10	33.3
Pan chewing	No	28	93.3
	Yes	2	6.7
Diagnosis	Hypopharynx	2	6.7
	Larynx	1	3.3
	Nasopharynx	2	6.7
	Oral cavity	19	63.3
	Oropharynx	5	16.7
	Unknown Primary	1	3.3
Chemo cycle	Weekly	17	56.7
	3 Weekly	13	43.3
Radiation	Adjuvant	13	43.3
	Definitive	17	56.7

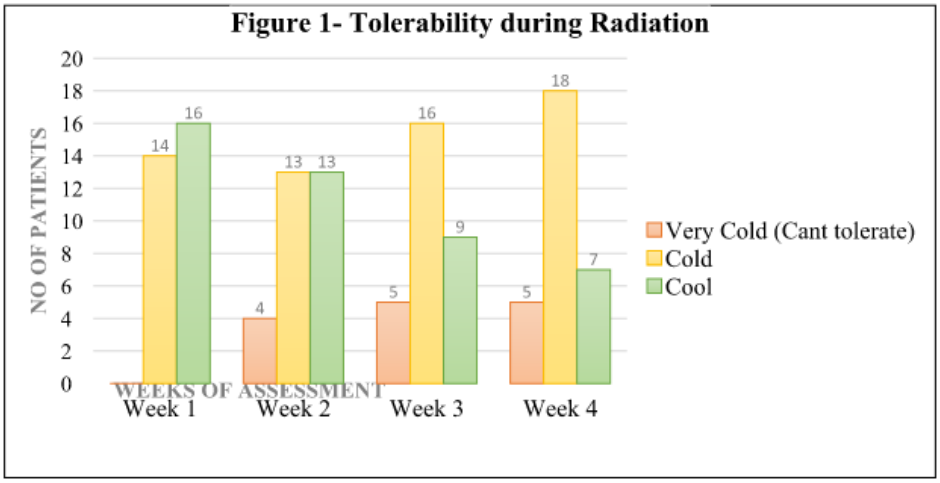
The great majority of the subjects included in the study are in the average age of 50±11; 100% were male. There were about total of 76.7% who had habits like 63.3% had tobacco chewing habit and alcohol consumption, 16.7% had smoking, and 6.7% had habit of pan chewing whereas there were 23.3% who had no habits of any form. Of the subjects participating in the study, 63.3% were diagnosed with cancer of oral cavity, 16.7% had cancer of oropharynx, 6.7% had cancer of hypopharynx, 6.7% had cancer of nasopharynx, 3.3% had cancer of larynx and 3.3% had cancer of unknown primary. 56.7% patients received weekly cisplatin whereas 43.3% patients received 3 weekly cisplatin. 43.3% patients received adjuvant radiation therapy whereas 56.7% patients received definitive radiation therapy.

Tolerability of oral cryotherapy

Evaluation of tolerability of oral cryotherapy for radiation is illustrated in Figure 1.

Intolerance to oral cryotherapy- From week 1 to week 4, total of 5 (16.7%) patients found oral cryotherapy as very cold and couldn't tolerate the intervention.

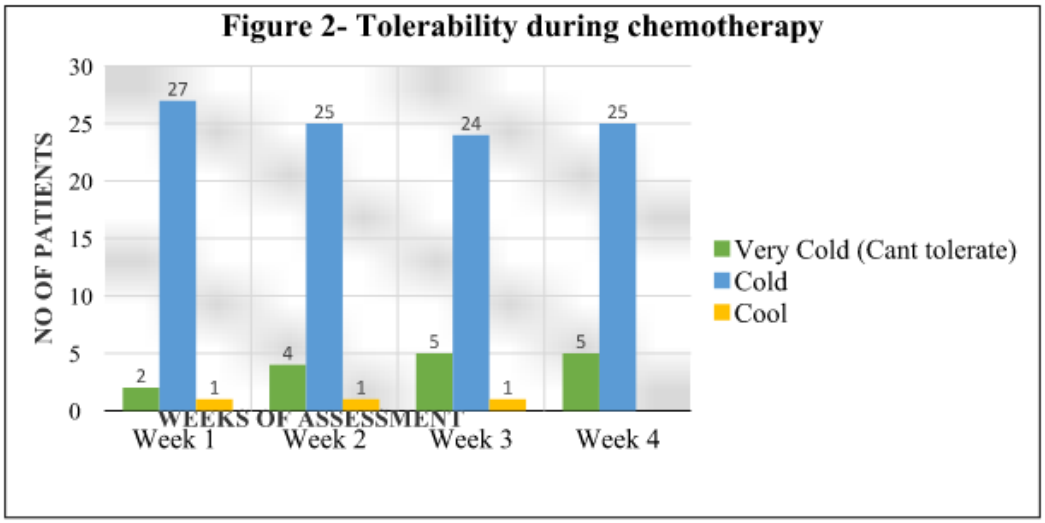
Tolerance to oral cryotherapy- In week 1, 14 (46.7%) patients found oral cryotherapy cold and 16 (53.3%) patients found it cool. During week 2, 13 (43.4%) patients found it cold and 13 (43.4%) patients found it cool. During week 3, 16 (53.3%) patients found it cold and 9 (30%) patients found it cool. During week 4, 18 (60%) patients found it cold and 7 (23.3%) patients found it cool.



Evaluation of tolerability of oral cryotherapy for chemotherapy is illustrated in Figure 2.

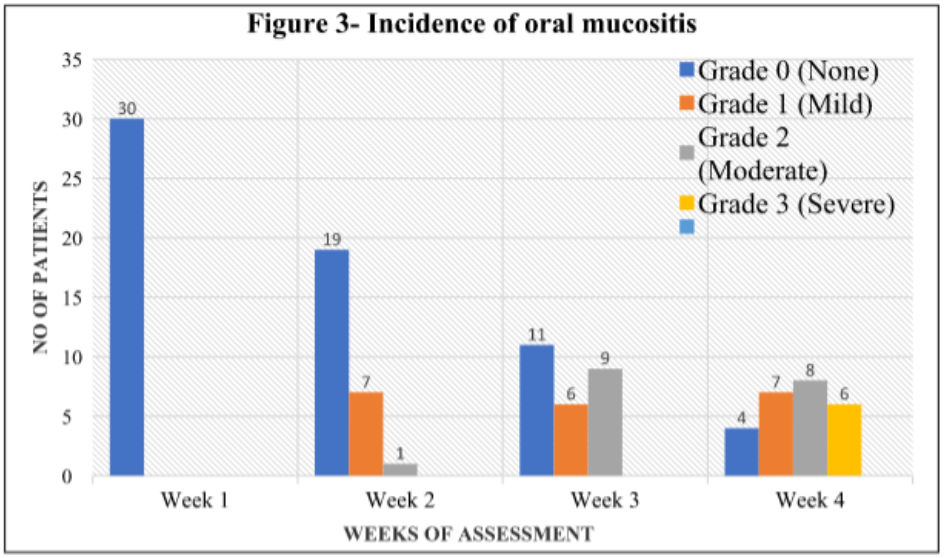
Intolerance to oral cryotherapy- From week 1 to week 4, total of 5 (16.7%) patients found oral cryotherapy as very cold and couldn't tolerate the intervention.

Tolerance to oral cryotherapy- In week 1, 27 (90%) patients found oral cryotherapy cold and 1 (3.3 %) patient found it cool. During week 2, 25 (83.3%) patients found it cold and 1 (3.3 %) patient found it cool. During week 3, 24 (80.0%) patients found it cold and 1 (3.3 %) patient found it cool. During week 4, 25 (83.3%) patients found it cold.



Incidence of oral mucositis for oral cryotherapy

It is represented in Figure 3. During week 1, 30 patients (100%) had no mucositis. During week 2, 19 patients (70%) had no mucositis, 7 patients (25%) had grade 1 oral mucositis, 1 patient (3.6%) had grade 2 oral mucositis. During week 3, 11 patients (42.3%) had no mucositis, 6 patients (22.2%) had grade 1 oral mucositis, 9 patient (33.3 %) had grade 2 oral mucositis. During week 4, 4 patients (16%) had no mucositis, 7 patients (28%) had grade 1 oral mucositis, 8 patient (32%) had grade 2 oral mucositis and 6 patients (24%) had grade 3 oral mucositis. During week 1 to week 4, there was no grade 4 oral mucositis seen.



Pain score and use of pain medication

Table 2. Analysis based on distribution of subjects as per pain assessment using VAS and use of pain medication

Pain score	**Week 1**		**Week 2**		**Week 3**		**Week 4**	
	Counts	Percent	Counts	Percent	Counts	Percent	Counts	Percent
None	30	100.0	22	81.5	12	46.2	5	20.0
Mild	0	0.0	5	18.5	6	23.1	10	40.0
Moderate	0	0.0	0	0.0	8	30.8	10	40.0
Total	30	100.0	27	100.0	26	100.0	25	100.0
Use of pain medication	**Week 1**		**Week 2**		**Week 3**		**Week 4**	
	Counts	Percent	Counts	Percent	Counts	Percent	Counts	Percent
No	30	100.0	23	85.2	7	26.9	2	8.0
Yes	0	0.0	4	14.8	19	73.1	23	92.0
Total	30	100.0	27	100.0	26	100.0	25	100.0

During week 1, 30 (100%) patients had no complaints of pain. In week 2, 22 (81.5%) patients had no pain, 5 (18.5%) patients had complaints of mild pain. In week 3, 12 (48.2%) patients had no pain, 6 (23.1%) patients had mild pain and 8 (30.8%) had moderate pain. In week 4, 5 (20%) patients had no pain, 10 (40%) patients had mild pain and 10 (40%) patients had moderate pain. During week 1 to 4, there was no complaints of severe pain.

It also represents use of pain medication. In week 1, 30 (100%) patients did not use pain medication. In week 2, 23 (85.2%) patients had no use of pain medication and 4 (14.8%) patients had use pain medication in some form. In week 3, 7 (26.9%) patients had no use of pain medication whereas 19 (73.1%) patients used some form of pain medication. In week 4, 2 (8%) patients did not use pain mediation while 23 (92%) patients used pain medication in some form.

Various parameters were assessed with change over time to find the significance of oral cryotherapy. Table 3 represents analysis of the parameters weekly assessed for change over time. Variables were not normally distributed, a non-parametric Friedman test was carried out to test the difference between related samples i.e., Baseline till post 4 weeks. Post-hoc Wilcoxon signed-rank test was performed with Bonferroni correction of alpha for pair-wise comparison of mean rank difference between baseline week 1 and post week 4 of the treatment by each of the parameters.

Table 3. Analysis of the parameters weekly assessed for change over time

Parameters	Weeks	Median (Q1, Q3)	P value*	Chi-square value	P value**	Z value	t value
Radiotherapy	1	3 (2, 3)	<0.001	25.39			7.81
	2	2 (2, 3)			0.038	-2.640	
	3	2 (2, 3)			0.003	-2.97	
	4	2 (2,2.3)			0.001	-3.27	
Chemotherapy	1	2 (2, 2)	NS	8.077			7.81
	2	2 (2, 2)			NS	-1.414	
	3	2 (2, 2)			NS	-1.732	
	4	2 (2, 2)			NS	-2.00	
RTOG grading	1	0 (0, 0)	<0.001	54.75			7.81
	2	0 (0, 1)			0.007	-2.714	
	3	1 (0, 2)			<0.001	-3.520	
	4	2 (1, 2)			<0.001	-4.069	
Pain score	1	0 (0, 0)	<0.001	52.51			7.81
	2	0 (0, 0)			0.025	-2.236	
	3	2.5 (0, 5)			0.001	-3.351	
	4	4 (2.5, 5.5)			<0.001	-3.949	

*: P value calculated from Friedman test to test overall week wise comparison
**: P value calculated from Wilcoxon signed rank test (to comparison with week 1)

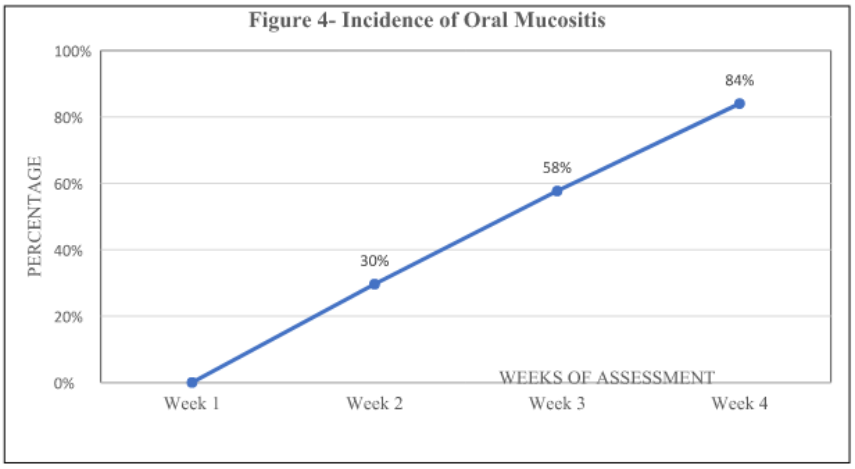
Radiotherapy- The comparison of Friedman calculated value (level of significance $p < 0.05$) revealed that oral cryotherapy during 4 weeks was tolerated effectively by the clients. The Wilcoxon calculated value was found to be significant at the (level of significance $p < 0.01$) on week 3 and week 4 when compared to week 1 but not at week 2 for clients receiving radiotherapy. Therefore, the null hypothesis (H_{01}) is rejected and H_1 is accepted for all 4 weekly observations.

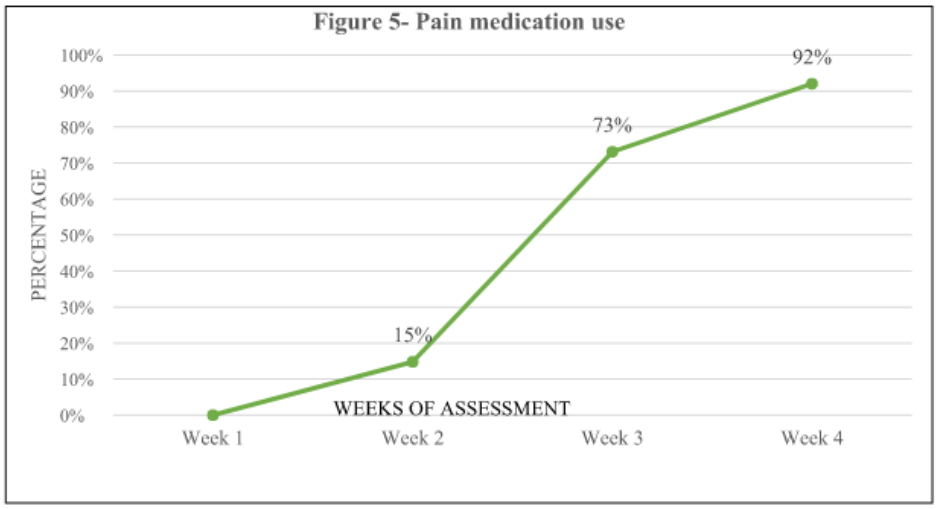
Chemotherapy- Tolerability during chemotherapy scores were compared over four weeks. The Friedman test was not significant (level of significance $p < 0.05$) revealed that oral cryotherapy during 4 weeks was not tolerable by the clients. The Wilcoxon calculated value was also not significant (level of significance $p < 0.01$). Null hypothesis (H_{02}) is accepted and H_2 is rejected for all 4 weekly observation.
This proves that Oral cryotherapy is tolerable for clients receiving radiotherapy.

RTOG grading- The comparison of Friedman calculated value (level of significance $p < 0.05$) revealed that oral cryotherapy during 4 weeks reduced the grades of oral mucositis of the clients. The Wilcoxon calculated value was found to be significant (level of significance $p < 0.01$) on week 2, week 3 and week 4 when compared to week 1 for clients receiving chemoradiotherapy.

Pain scores- The comparison of Friedman calculated value (level of significance $p < 0.05$) revealed that oral cryotherapy during 4 weeks reduced the pain scores of the clients. The Wilcoxon calculated value was found to be significant (level of significance $p < 0.01$) on week 3 and week 4 when compared to week 1 but not at week 2 for clients receiving chemoradiotherapy.

Trend test analysis for incidence of oral mucositis and use of pain medication is illustrated in Figure 4 and Figure 5.





V. Discussion:

Mucositis is common complication of radiotherapy of head and neck cancers. Treatment of mucositis is mainly based on supportive therapies, i.e., oral hygiene, consumption of adequate liquids, and use of mouth washes. Related studies have introduced various substances and agents as effective medications for reducing or limiting signs and symptoms of mucositis.

Demographics

The present study represents that all male patients were included in the study as head and neck cancer is most prevalent among male population. The average age was 50.97±11.55. Majority of the patients had no co-morbidities. There were about total of 23 (76.7%) patients who had habits like 19 (63.3%) had tobacco chewing habit, 10 (63.3%) patients had habit of alcohol consumption five (16.7%) patients had smoking, and two (6.7%) patients had habit of pan chewing whereas there were seven (23.3%) patients who had no habits of any form. 30 patients received concurrent chemoradiotherapy. These patients received radiation therapy to a dose of 66-70Gy/ 35# (definitive) or 60-66Gy/30-33# (adjuvant) along with concurrent chemotherapy cisplatin 40mg/m^2 weekly or 100mg/m^2 3 weekly. From 30 head and neck cancer patients, 19 (63.3%) patients had cancer of oral cavity, five (16.7%) patients had cancer of oropharynx, two (6.7%) patients had cancer of hypopharynx, , two (6.7%) patients had cancer of nasopharynx, one (3.3%) patients had cancer of larynx and one (3.3%) patients had cancer of unknown primary.

A prospective, cross-sectional study done by **Wuketich S, Hienz SA, Marosi C** to find the prevalence of Clinically Relevant Clinically Induced OM (CRCIOM) in outpatients receiving chemotherapy for solid tumors. In the CRCIOM group, 16 patients were male, and two were female; 8 patients with CRCIOM had received head and neck radiotherapy. A higher prevalence of CRCIOM was found in smoking patients ($p < 0.05$) and in the patients who have not had a dental check-up within the preceding 12 months ($p < 0.01$).[22] **Vera-Llonch et al.** conducted a retrospective study to evaluate the incidence and clinical impact of OM in 450 patients receiving radiotherapy for HNC, reporting the occurrence of OM in 83% of patients, among which29% of cases were severe. Severe OM was associated with treatment breaks and hospitalization, and was more likely to occur in patients with nasopharyngeal carcinoma or oropharyngeal tumors who received concomitant chemotherapy. **Elting et al** reported virtually identical incidence of OM in patients with oral cavity or oropharynx tumors (99 % overall; 85 % grade 3–4) and those with tumors of the larynx or hypopharynx (98% overall; 77% grade 3–4).In this prospective multicenter study, patients received a cumulative radiation dose of least 40 Gray (Gy) in single daily fractions, with or without subsequent boost and/or chemotherapy.

Tolerability of oral cryotherapy

In this study we demonstrated that oral cryotherapy was the treatment with a good compliance for radiotherapy. The results from the current study support that oral cryotherapy significantly tolerable to patients receiving radiotherapy. The duration of chemotherapy in this study did not prove 40-minutes-long cryotherapy to be tolerable. However, there were no studies done specific for tolerability of oral cryotherapy being done.

Effectiveness of oral cryotherapy in terms of incidence of OM, pain scores and use of pain medication

In this study, Oral cryotherapy was proven to be significantly effective in augmenting the number of patients who were free from oral lesions, as well as in diminishing the pain scores and the use of pain medications in all 4 weeks.

In a study conducted by **Noronha et al.** stated that even concurrent chemoradiotherapy are well tolerated by patients and oral mucositis is among them an uncommon adverse effect. Acute toxicities of grade 3 or higher occurred in 71.6% of patients in the once-a-week arm and in 84.6% of patients in the once-every-3-

weeks arm, specifically 43% patients experience Grade 3-5 mucositis. Hence it is of major importance, as patients with oral mucositis progressively become unable to eat solid or even liquid food, since chemoradiotherapy- induced oral mucositis is extremely painful and fails to respond to topical anesthetics or common systemic analgesic drugs.[23] **Salvador et al.** in 2012 suggested that oral cryotherapy and an oral care protocol seem to be successful in reducing the severity of OM compared with an oral care program alone.[24] **Vokurka et al.** found that incidence of OM was greatly lower in the cryotherapy group.[25] They noted that reduced oral tissue damage which is mediated by oral cryotherapy did not appear to lead to reduction in the fevers of unknown origin and intravenous antibiotic use. Similar results were seen in study by **Nikoletti S et al**.[26] This shows that cryotherapy has better control over pain. This is in accordance to Mahood DJ et al. This study results revealed that cryotherapy is an effective method for reducing pain severity and mucositis in patients with head and neck carcinomas, undergoing radiotherapy.[27] **Mahood et al**. states that oral cryotherapy reduced the salivary secretion of anticancer agents into the mucosa by the mechanism of a local vasoconstriction. A study conducted by **Svanberg et al**. revealed that oral cryotherapy has been shown to effectively reduce the incidence and severity of mucositis in patients receiving myeloablative treatment.[10] A Cochrane systematic review assessed the articles on mucositis and oral candidiasis. According to this report, among 6 prophylactic agents for mucositis, ice chips were the only effective factor.[28] In this way, cryotherapy has been introduced as an effective therapy, but the evidence that it prevents mucositis is still inadequate and unreliable.

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