



Effect of Flavored (Honey and Tulsi) Ice Chips on Reduction of Oral Mucositis among Children Receiving Chemo Therapy

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ABSTRACT

Oral mucositis is probably the most prevalent, debilitating complication of cancer treatments particularly chemotherapy and radiation. It can lead to several problems, including pain, nutritional problems, and increased risk of infection due to open sores in the mucosa. The aim of this study was to investigate the effect of flavored (honey and tulsi) ice chips Vs plain ice chipson oral mucositis following chemotherapy. A randomized controlled trial was conducted on 40 ALL patients who underwent chemotherapy. The patients were randomly divided into two groups of 20 each. The first group was instructed to place plain ice chips and second group the flavored ice chips in their mouth just 5 minutes before to each dose of methotraxate, continuously swish the ice inside their mouth, and refill the ice chips before the previous ice had completely melted for a period of 30 minutes during the study period. Oral examinations were performed on the 5th and 15th days of the study. Severity of oral mucositis was evaluated by a WHO mucositis scale at the above-mentioned intervals. There was highly significant decrease in the occurrence of oral mucositis observed in both the groups but more in the children receiving flavored ice chips at $p < 0.001$ in 5th day and 15th day of assessment than the plain ice chips. Although not much significant difference was observed in severity of mucositis between the two groups but the flavored ice cube made up of honey and tulsi was more effective in reduction of oral mucositis.

Keywords: Oral mucositis, plain ice chips, flavored ice chips, chemotherapy.

INTRODUCTION

Oral mucositis is one of the most recurrent and potentially severe complications of chemotherapy which has a significant impact on patient's quality of life. While the management of other chemotherapy-related toxicities has improved, but the incidence of mucositis is still increasing.

The epithelial cells of the oral mucosa encounter rapid turnover, usually every 7 to 14 days, which makes these cells susceptible to the cytotoxic effects of the therapy. The maturity and cellular growth of epithelial cells get affected by both chemotherapy and radiation therapy causing changes to normal turnover and cell death.

Cancer patients receiving chemotherapy usually become symptomatic four to five days after beginning treatment, reaching a peak at around day 10, and then slowly improving over the course of a few weeks. Radiotherapy induced mucositis usually appears at the end of the second week of treatment and may last for six to eight weeks. As a result of cell death, after chemo therapy and radiation therapy, the mucosal lining of the mouth becomes thin, may slough off and then become red, inflamed and ulcerated. The ulcers may become covered by a yellowish white fibrin clot called a pseudomembrane¹.

The incidence and severity of mucositis vary from patient to patient. It is estimated that there is 40% incidence of mucositis in patients treated with standard chemotherapy

The risk of oral mucositis among cancer patient increases depending on the type of treatment they receive. The gentler chemotherapeutics have lowest risk while more aggressive agents like fluorouracil and cisplatin have higher risk to develop oral mucositis. The incidence rate of oral mucositis is 90%. Individuals treated with standard chemotherapy regimens have up to 70% risk of developing oral mucositis².

The incident of oral complications and treatment-related consequences are higher in aggressive cancer therapy. Unfortunately, prevention and/or treatment of such oral sequelae have often become under looked as priorities of the treatment team. Effective strategies for the prevention or treatment of oral mucositis have not been standardized, and vary considerably among institutions. Improvement of oral status and therapeutic administration of cold should be practiced as a prophylactic measure to prevent oral inflammation.³

Putting and sucking ice cubes or ice chips in the mouth was often recommended as a way of providing relief from the symptoms of oral mucositis. However cryotherapy, rapid cooling of oral cavity using ice cubes can cause the blood vessels to constrict, and hence reduces blood flow to the oral mucosa⁴. By this it reduces the amount of chemotherapeutic drug reaching the oral mucous membranes and decreases the local cytotoxic activity of these drugs and thus reduces oral mucositis^{5,7}.

Recent studies support and confirm the use of cryotherapy as a cheap and effective method of



minimizing 5-fluorouracil induced mucositis among cancer patients, but it is not effective for continuous infusions of such chemo therapeutic agents.^{6, 8, 9, 10, 17}

Severe mucositis is a common cause of morbidity in pediatric and adolescent patients receiving chemotherapy. High symptoms burden may have a profound impact on patient's quality of life and their level of psychological distress. Application of oral ice cubes is an effective method of minimizing the symptoms of oral mucositis⁸.

Instead of using simple plain ice cube, investigator tried to investigate the effect of ice cubes made up of honey and tulsi because of their anti-inflammatory and anti-cancer potentiality of both the compound for reduction of oral mucositis.

Holy basil is a powerful anti-inflammatory agent and a natural healer, and often known as "the Mother medicine of nature" in Ayurveda. Due to the strong evidence of anti-stress and anticancer effects the Holy basil is included in modern herbalist call –as having the "adaptogen" effect.¹¹

Holy basil can act as a COX-2 inhibitor – which decreases inflammation, pain and can repair cells damaged by oxidation and radiation and has the potential to destroy pre-cancerous lesions and tumors.¹¹

The active constituent in holy basil leaf, eugenol is responsible for its anticancer potential which inhibits the multiplication, migration and invasion of cancer cells and will also induce apoptosis (programmed cell death of tumors).

According to recent studies these compounds increases the antioxidant activity and destroys cancer cells. It was shown that flavonoid compounds in water extracts of holy basil, orintin and vicenin protected mice against radiation-induced tumor. *Ocimum sanctum* (Tulsi) has the ability to protect the DNA of the body from dangerous radiation.¹¹⁻¹⁴ The flavonoids namely orientin and vicenin isolated from OS leaves shows better radio protective effect as compared with synthetic radio protectors. They have shown significant protection to the human lymphocytes against the clastogenic effect of radiation at low, non toxic concentrations.¹⁵

Clinical research has also shown that medical-grade honey can destroy pathogens causing food-borne illness such as *Escherichia coli* and *salmonella*. Honey has also shown promising effect in fighting bacterial strains causing resistance to antibiotics. Research has shown that honey is effective against methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* and fights infections against pathogens on many levels making it difficult to develop resistance to it. Antibiotics by contrast, typically target bacteria while they are growing, giving them an opportunity to evolve resistance. Honey reduces the virulence of bacterial pathogens, and allows antibiotics to take effect.¹²

Furthermore there is less research evidence of development of oral mucositis after administration of chemotherapeutic agent methotrexate, but during the clinical experience the investigator had observed that there is development of oral mucositis as a side effect of methotrexate. So the main aim of the present study is to compare the effect of plain ice cube with the ice cube made up of tulsi and honey in reduction of oral mucositis induced by methotrexate.

MATERIALS AND METHODS

The randomized control trial was conducted at a hemato oncology unit of a tertiary care institute of Odisha. It was conducted from February 2015 to May 2015, following Ethical approval from the ethical committee. Children between 5-19 years who were receiving methotrexate and without having oral mucositis prior to administration of mthotrexate were eligible for inclusion.

Enrolled children were randomized to two groups either to receive Plain ice cubes or flavored ice cube made up of honey and tulsi. Written informed consent was taken prior to the enrollment from the parents of the participant. On the first day, administration of plain and flavored ice cube was done to the children. The first group was instructed to place plain ice chips and second group the flavored ice chips in their mouth just before 5 minutes to each dose of methotrexate, continuously swish the ice inside their mouth, and replenish the ice chips before the previous ice had completely melted. This was done for a period of 30 minutes. The follow up was done on the 5th and 15th day of administration of plain and flavored ice cubes. Severity of oral mucositis was evaluated by a WHO mucositis scale at the above-mentioned intervals.

Sample size

Most of the children in the hemato oncology unit were receiving 5 Floro Uracil and less number of children were receiving methotrexate as chemo therapy. To achieve an effect size of 30% with an α error of 0.05 and power of 80% we planned a sample size of 64. But due to less availability of patients receiving methotrexate finally we enrolled 40 children in our study time frame. The revised sample size was approved by the research committee.

Statistical test: - Descriptive & inferential statistics were utilized for the analysis of the data. The level of significance set for testing the hypothesis was 0.05 using 't' test & chi square test.

Table 1 depicts that majority of 40% children were between 6-10 yrs old. As per gender, 60% were male and 40% were female.



RESULTS

Table 1: Description of Study Sample as per Demographic Variable

Sample characteristic		N (%)
Age	6-10yrs	16(40%)
	11-14yrs	13(32.5%)
	15-18yrs	11(27.5%)
Gender	Male	24(60%)
	Female	16(40%)
Duration of Exposure to chemotherapy	5yrs	2(5%)
	4yrs	6(15%)
	3yrs	17(42.5%)
	2yrs	9(22.5%)
	1yr	6(15%)

There was a significant reduction in the occurrence of oral mucositis observed in the group receiving honey and tulsi

Table 2: Comparison of grade of oral mucositis between children receiving flavored and plain ice cubes as per who mucositis scale N=40

Day of Assessment	Flavored (Honey and Tulsi) Ice cube			Plain ice cubes		
	Mild – moderate	Severe	Total (n %)	Mild- Moderate	Severe	Total (n %)
5 days	8	0	8 (40%)	13	5	18 (90%)
15 days	3	0	3 (15%)	16	0	16 (80%)

Table 3: Comparison of the effectiveness on plain and flavored ice cubes on severity of oral mucositis by using mean, sd, un paired t – test, p value N=40

Criteria	Plain Ice cube	Flavored (Honey and tulsi) ice cubes	Mean difference	Un paired T value	DF	P value
	Mean ± SD	Mean ± SD				
5 days	1.75 ± 0.96	0.4 ± 0.50	1.35	5.54	38	0.001*
15 days	1.1 ± 0.71	0.15 ± 0.36	0.95	5.26	38	0.001*

Oral cryotherapy has a significant contribution to the protection of oral health by reducing mucositis. Application of non-pharmacological measures like ice cube reduces the occurrence of oral mucositis by vasoconstriction. More ever recent studies show the anti-cancer and anti-inflammatory effect of tulsi and honey. The result of the present study reveals that there was highly significant decrease in the occurrence of oral mucositis observed in the children treated with flavored (honey and tulsi) ice cubes than plain ice cubes at $p < 0.001$ on 5th day as well as on 15th day following chemo therapy.^{13, 14, 18}

Present study supports to the similar study conducted by Castellino Flavio (2008) where they have reported the similar findings that there was significant reduction in incidence of oral mucositis among the children receiving flavored ice cubes than plain ice cubes on 5th day and 15th day at $p = 0.001$. But a study conducted by Rocke LK et al.

ice cube compared to plain ice cube (0.4 ± 0.50 vs. 1.75 ± 0.96 , unpaired t test 5.54 at $p = 0.001$) on 5th day of assessment and 15th day (0.15 ± 0.36 Vs 1.1 ± 0.71 , unpaired t test 5.26 at $p = 0.001$) Incident of oral mucositis was significantly less in the group receiving honey and tulsi ice cubes 8 (40%) as compared to the group receiving simple plain ice cubes 18 (90%) on 5th day of assessment following chemo therapy as well as on 15th day of assessment (15% Vs 80%).

DISCUSSION

In the view of magnitude of the problem, an increase rate of oral mucositis is seen in patient with hematology malignancies that receiving stomatotoxic agents like methotraxate as major side effect. Severe mucositis is a common cause of morbidity in school going and adolescent children undergoing chemotherapy.

(1993) reported in their study that there was no significant difference in occurrence of oral mucositis with plain and flavored ice cubes rather both are equally effective in reducing oral mucositis.^{6, 16, 17, 19}

CONCLUSION

Oral cryotherapy is simple and inexpensive method of treating oral mucositis. Moreover it does not endanger the efficacy of chemotherapy, as it is based on topical vasoconstriction. To conclude, the results of our study strongly support that cryotherapy inhibits methotrexate induced stomatitis in a statistically significant manner. Though both plain ice cube as well as flavored ice cubes made up of honey and tulsi is effective in reduction oral mucositis but The present study findings reveals that the flavored ice cubes (honey and tulsi) is more effective than plain ice cubes in reduction of oral mucositis in the patient receiving methotraxate. Flavored ice cubes can be incorporated to routine practice in pediatric oncology



setting as it is easy to prepare and cheaper in prevention of occurrence of oral mucositis in the next cycle among the children undergoing chemotherapy.

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