

Efficacy of Improvised Topical Zinc (1%) Ora-Base on Oral Mucositis during Cancer Chemo-Radiation—A Randomized Study

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Summary Oral mucositis refers to erythematous and ulcerative lesions of oral mucosa during chemo/radiotherapy. Treatment modalities were directed towards reduction in severity of oral mucositis. Zinc plays an important role to retard oxidative processes and is considered as the critical component in wound healing. To compare the efficacy of zinc alone with improvised zinc preparation in reducing the severity of oral mucositis. Improvised zinc was a combination of zinc oxide, amla, tulsi and curcumin at 1% therapeutic concentrations. Seventy-five subjects undergoing chemo/radiotherapy were randomly divided into three groups: Group A (25 subjects) had received topical 5% zinc oxide paste trice daily application after food for entire treatment period, initiated 2 d prior to radiotherapy. Group B (25) received improvised zinc preparations (1%) and instructed to apply same as group A. Group C (25) received standard treatment offered by cancer hospital. All the groups were assessed for oral mucositis using WHO grading system at 7th, 14th, 21st, 28th, 35th day by the oncologist and results were tabulated for statistical analysis. Severity of oral mucositis reduced in zinc and improvised zinc group ($p=0.096$) when compared with controls with significant p value (0.037). Comparison of improvised zinc preparation (1%) group with only zinc group revealed that severity of overall mucositis though was not significant, was less in improvised zinc group with p value (0.029, 0.013) at 28 and 35 d respectively. Improvised zinc administration during radiation therapy was beneficial in reduction of oral mucositis during cancer treatment.

Key Words zinc oxide, mucositis, chemoradiation, grading of mucositis, curcumin, amla, tulsi

Oral mucositis is the dose limiting side effect observed in patients with head and neck cancer being treated with chemotherapy and/or with radiation therapy to fields involving the oral cavity (1). Signs and symptoms of oral mucositis, include severe pain which may lead to dose reductions and unplanned interruptions of chemotherapy and/or radiotherapy, and often affect patient's quality of life. In addition, ulcerative mucositis represents a risk factor for local or systemic infectious complications that may be life threatening in immunosuppressed patients (2).

Clinical features of mucositis and its severity of mucosal destruction in radiation patients are dose-dependent. Hyper keratinization occurs after a cumulative dose of 10–20 Gy, leading to generalized whitening of mucosal tissues. After 1 wk of therapy, more than 20 Gy results in patchy erythema. After 2 to 3 wk of radiation therapy (or approximately 30 Gy), mucosal atrophy, ulcer-

ation, edema, and a more uniform erythema are present, accompanied by pseudomembranous fibrin clot formation (3).

Signs and symptoms of mucositis persist until 2 to 6 wk following the completion of therapy. Oral mucosal changes are evident after 2 to 4 d of chemotherapy, erythema occurs 5 to 8 d after therapy, edema and ulceration occur 2 d later. Symptoms usually persist for 7–10 d (3).

Zinc plays an important role in maintenance of epithelial and tissue integrity through promoting cell growth and suppressing apoptosis (4). Zinc is an essential intracellular mineral of “exceptional biologic and public health importance” with important enzymatic cofactor activities for cell membrane stability, DNA and RNA structure. At the cellular level, zinc is critical for cell survival, affecting signal transduction, transcription, and replication. Zinc, thus plays an essential role in growth, immune function, proteoglycan synthesis, antioxidant defense, formation of collagen and a critical

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component in the healing wound. Zinc ability to retard oxidative processes has long been recognized (5).

Several studies investigated the role of oral zinc in chemotherapy-induced oral mucositis. Few of them supported the idea that zinc has the potential of reducing incidence and severity of chemotherapy-induced oral mucositis in cancer patients (6).

Oral or topical use of curcumin has been reported to be effective in wound repair in normal and diabetic individuals. It is believed to be possessing inhibitory activity against hydrogen peroxide-induced oxidative damage in human—keratinocytes and fibroblasts. Curcumin has also been reported to have potent antioxidant activity and to confer protection against radiation in-vitro and in-vivo (7).

Tulsi (*Ocimum sanctum*) has an excellent anticancer property. Detoxification of carcinogens and mutagens carried out by enzymes such as glutathione-S-transferase, cytochrome b5 and cytochrome P450, and aryl hydrocarbon hydroxylase is modulated by the alcoholic extract (AIE) of leaves of *Ocimum sanctum* (8). Tulsi has been shown to have antioxidant properties, which may be responsible for faster wound healing.

Amla had antioxidant property, so that protects cells against free radical damage. Amla is used to treat skin disorders, respiratory infections and premature aging and also useful in treating hemorrhage, diarrhea, dysentery, diabetes. It had antibacterial and astringent properties to prevent infection and help in the healing of ulcers (9).

The present study was carried out by incorporating all the above ingredients as improvised zinc, to assess its efficacy on oral mucositis. Thus the improvised zinc is the combination of zinc oxide, amla, tulsi and curcumin.

MATERIALS AND METHODS

The study was designed with an objective to reduce the severity of oral mucositis by topical zinc application vs only zinc intervention without any modifications and to assess the grading of oral mucositis by WHO grading system.

The study protocol was approved by institutional reviewed ethical board (ECR/227/INST/AP/2013/RR-16) and study was conducted at MNJ Institute of Oncology, Research Center Telangana.

A total of 75 subjects who were under chemo/radiotherapy for oral cancers above 18 y were included in the study receiving 60–70 Gy units of radiotherapy and cisplatin 50 mg.

The patients were randomly divided into three groups: Group A were the interventional group which comprised of 25 patients who received topical 5% zinc oxide paste trice daily application after food for entire period of chemotherapy+radiotherapy, which was initiated 2 d prior to radiotherapy. Group B were 25 patients who received improvised zinc preparations (1%) and instructed to apply same as group A. Group C were controls who comprised of 25 patients receiving standard treatment offered by cancer hospital. All the groups were assessed for oral mucositis using WHO grading

system at 7th, 14th, 21st, 28th, 35th day respectively by the oncologist and results were tabulated for statistical analysis.

WHO grading system for oral mucositis

Grade 0=No oral mucositis

Grade 1=Erythema and soreness

Grade 2=Ulcers, able to eat solids

Grade 3=Ulcers, requires liquid diet (due to mucositis)

Grade 4=Ulcers, alimentation not possible (due to mucositis)

RESULTS

Data was analyzed by SPSS software version and graft pad prism software 6.0 version. Data was summarized by mean \pm SD for continuous data and percentages for categorical data. The comparison between three groups was done by one way ANOVA test and followed by post hoc multiple comparisons test. The comparison between three groups was done by chi-square test for categorical data. All *p*-values less than 0.05 were considered as statistically significant.

Demographic results

The present study demonstrated that the incidence of head and neck cancers were observed at average age between 55.4 ± 12.4 y in zinc group followed by control group were 53.96 ± 14 and in improvised zinc group, 46.12 ± 12.96 . The incidence of head neck cancers were high in males (65%) when compared to females (35%) in the ratio of 2 : 1 in all the groups.

Buccal mucosal carcinoma dominated the type of cancer. The individuals suffered followed by carcinoma of tongue and floor of the mouth.

Comparison of zinc ora base vs controls

When comparing the zinc group and control group the severity of grade 2 mucositis was less in zinc group at day 7 (*p*=0.166) and day 14 (*p*=0.308) which was not statistically significant. The severity of grade 2 mucositis gradually increased in zinc group at day 21 and day 28 with statistical significance (*p*=0.029) followed by similar findings observed in both zinc group and control group at day 35.

The severity of grade 3 mucositis was less in zinc group than control group at day 7 followed by similar results on days 14, 21 and 28, and gradually increased in the zinc group at day 35 (*p*=0.013). The severity of grade 4 mucositis was less in zinc group at day 14, 21, 28 and day 35 compared with control group with *p* value significant (0.037).

Comparison of zinc group and control group reveals that severity of overall mucositis was decreased in zinc group when compared with control group.

Comparison of improvised zinc (zinc+ayurvedic) preparation group vs controls

When comparing improvised zinc group and control group, the severity of grade 2 mucositis was less in improvised zinc group at day 7 (0.040), day 14 (0.167), day 21 (0.091) and day 28 (0.017) and control group at day 35 (0.008) which were not statistically significant. The severity of grade 3 was less in improvised zinc group when compared to control group at day 21, day

Table 1. Comparison between zinc group, improvised zinc group and control group.

| Time point | Groups | n | Normal | Erythematous | Ulcerations | Liquid diet | Intravenous | Discontinued | Death | p-value |
|------------|-----------------|----|--------|--------------|-------------|-------------|-------------|--------------|-------|---------|
| Base line | Zinc | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | NA |
| | Improvised zinc | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | |
| | Control | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Day 7 | Zinc | 25 | 17 | 8 | 0 | 0 | 0 | 0 | 0 | 0.040 |
| | Improvised zinc | 25 | 13 | 9 | 0 | 0 | 0 | 0 | 0 | |
| | Control | 25 | 12 | 10 | 3 | 0 | 0 | 0 | 0 | |
| Day 14 | Zinc | 25 | 8 | 12 | 4 | 0 | 0 | 1 | 0 | 0.167 |
| | Improvised zinc | 25 | 5 | 12 | 5 | 0 | 0 | 0 | 3 | |
| | Control | 25 | 4 | 15 | 4 | 2 | 0 | 0 | 0 | |
| Day 21 | Zinc | 25 | 2 | 10 | 11 | 1 | 0 | 1 | 0 | 0.091 |
| | Improvised zinc | 25 | 3 | 4 | 10 | 2 | 3 | 0 | 3 | |
| | Control | 25 | 3 | 7 | 11 | 4 | 0 | 0 | 0 | |
| Day 28 | Zinc | 25 | 0 | 12 | 10 | 2 | 0 | 1 | 0 | 0.017 |
| | Improvised zinc | 25 | 3 | 5 | 8 | 2 | 4 | 0 | 3 | |
| | Control | 25 | 3 | 7 | 10 | 5 | 0 | 0 | 0 | |
| Day 35 | Zinc | 25 | 0 | 6 | 16 | 2 | 0 | 1 | 0 | 0.008 |
| | Improvised zinc | 25 | 2 | 8 | 5 | 3 | 3 | 0 | 4 | |
| | Control | 25 | 3 | 6 | 7 | 7 | 0 | 0 | 0 | |

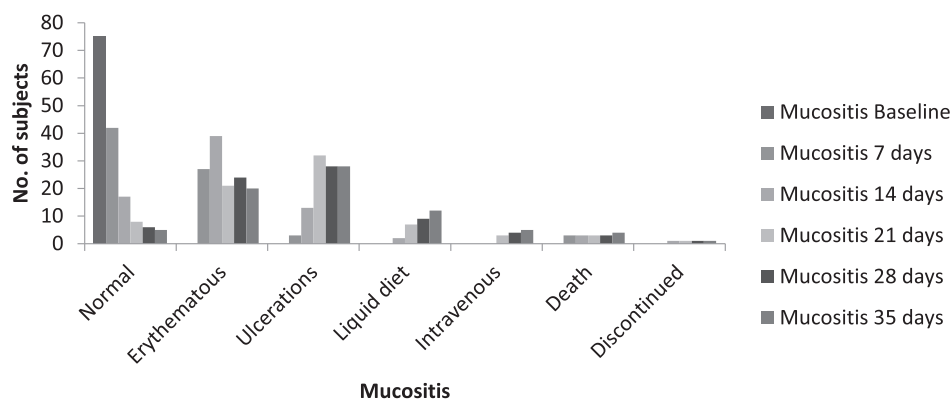


Fig. 1. Graphical representation showing comparison between overall mucositis.

28 and day 35 during overall treatment period. However, the grade 4 mucositis severity was greater in few patients between the two groups at day 21, day 28 and day 35.

Hence, the study demonstrated that severity of overall mucositis was less in improvised zinc group when compared to controls.

Comparison of improvised zinc preparation (zinc+ayurvedic) group vs zinc group

When comparing the zinc and improvised zinc preparations, with p values considered <0.05 , the severity of grade 2 mucositis was less in zinc group than the improvised zinc group at day 7 ($p=0.166$). At day 14, the severity was similar in both the groups ($p=0.308$) and at day 21 ($p=0.118$) and day 28 ($p=0.029$). Severity was gradually decreased in improvised zinc group than zinc

group. At day 35 severity of oral mucositis increased in improvised zinc group when compared with zinc group which was statistically significant ($p=0.013$). There was a gradual increase in severity of grade 3 mucositis, observed in zinc group at day 21, 28 and 35. The severity of grade 4 mucositis decreased in zinc group at day 21 and day 35 compared to improvised zinc group. At day 28, the severity was similar in both the groups.

Thus the study revealed that severity of overall mucositis though it was not significant it was less in improvised zinc group when compared with zinc group (Table 1).

Figure 1 represented total number of subjects suffering from different stages of oral mucositis starting from baseline to 35 d of chemo-radio therapy. The graph represents that grade 1 mucositis was present in almost in

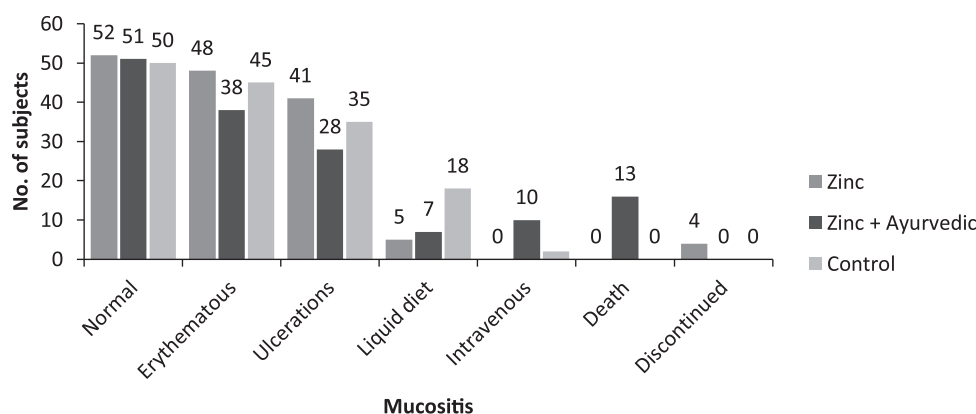


Fig. 2. The cluster bar diagram for the comparison between zinc, zinc+ayurvedic, control for the parameter mucositis overall.

all subjects at baseline and reduced from day 7 to day 35.

Grade 3 mucositis severity was high at day 21 and reduced by day 35.

Figure 2 represented total number of subjects in all the three groups with different stages of oral mucositis. Patients with grade 2 mucositis and grade 3 mucositis were less in zinc+ayurvedic group when compared with zinc group and control groups. Most of the patients in zinc+ayurvedic group were under intravenous treatment. Additionally 13 members died during treatment. There were some death of patients noticed during treatment period.

DISCUSSION

Head and neck cancer was mostly observed at the average age of 55.4 y with more male predilection. Ninety-five percent of patients with head and neck cancer were treated by chemo/radiotherapy. Oral mucositis is the dose limiting side effect observed in the patients with head and neck cancer being treated with chemotherapy and/or radiation therapy, which was consistent with the study by Stoyanov et al., who reported that the incidence of head and neck cancers were seen in 4–6 decades of life with more male predilection.

Zn is an antioxidant, stabilizer of DNA and organelle structure. It acts as an important co-factor for the synthesis of DNA and as a component helps to wound healing. It has anti-inflammatory effect and used as immune system modulator. Based on these properties, zinc may have preventing role in decreasing radiation induced side effects.

Lin et al. (10) conducted a study to determine if zinc supplementation could accelerate the healing of mucositis after radiotherapy. Patients in the control group developed grade 2 mucositis and dermatitis sooner than patients in the experimental group. There was also significant difference in the development of grade 3 mucositis and dermatitis between 2 groups (10).

Moslemi et al. conducted a study in both zinc and control groups, mucositis was evident during the first week but its prevalence was 40.5 and 70.5% in the zinc and placebo groups respectively at the end of this

period with significant difference ($p < 0.0001$). In 2–7 and 8 wk, the severity of oral and pharyngeal mucositis were lower in the zinc group, with p value of < 0.003 (11).

Mosalaei et al. stated that according to their study oral mucositis scores were less severe in the zinc group in weeks 4 to 6. The difference was statistically significant and the p values for weeks 4, 5 and 6 were 0.02, 0.007, and 0.012, respectively (12).

Mansourian et al. conducted a study in 37 patients with *Curcuma longa* and was found that development grade 3 mucositis was decreased in intervention group. *Curcuma longa* was found effective in reducing the symptoms of oral mucositis in patients undergoing radiotherapy in head and neck cancers by its anti-inflammatory and antioxidant effects (7).

Patil et al. evaluated the efficacy and safety of curcumin mouthwash in comparison with chlorhexidine in the management of oral mucositis. Curcumin was found to be better than chlorhexidine mouthwash in terms of rapid wound healing and better patient compliance. No oral or systemic complications were reported in this study (13).

Above studies shown that zinc and curcumin shown better effect in reducing severity of oral mucositis, in this study, severity of grade 2 oral mucositis decreased in the patients who received improvised zinc and the severity of grade 3 oral mucositis was decreased in the patients receiving topical zinc and severity of grade 4 mucositis was decreased in zinc group at day 21 and day 35 compared to improvised zinc group.

In a study to assess the potential of alcoholic and aqueous extracts in wound healing in Wistar albino rats, the rats were treated with two different doses each of alcoholic and aqueous extract of tulsi (*Ocimum sanctum*). Both the doses of alcoholic and aqueous extract significantly increased wound breaking strength, hydroxyproline, hexuronic acid, hexosamines, superoxide dismutase, catalase, reduced glutathione and significantly decreased percentage of wound contraction and lipid peroxidation when compared with the control group. The results from this study shows that *Ocimum sanctum* has antioxidant properties, which may be responsible

and favorable for faster wound healing and this plant extract may be useful in the management of abnormal healing (14).

Monga et al. evaluated the anti melanoma and radio protective activity of *Ocimum* in Swiss albino mice. The PnAq extract of *Ocimum* caused a substantial decline in tumor volume, increase in average body weight, and survival rate of mice. The extracts exhibited modulatory effect against radiation-induced chromosomal damage, induced an increase in reduced GSH level and GST activity (15).

Above animal studies showing that tulsi is effective in promoting wound healing similarly in this study tulsi reduces mucositis by its antioxidant property.

CONCLUSION

Zinc is beneficial in decreasing the severity of radiation-induced mucositis and oral discomfort. These results should be confirmed by additional evaluation in randomized studies with a larger number of patients. It was concluded that improvised zinc administration during head and neck radiation therapy produced significant benefit in relieving radiation-induced oral mucositis.

Disclosure of state of COI

Authors declare no conflict of interest.

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