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Evaluation of Efficacy and Safety of Zinobliss (Zinc Carnosine 2% and Lignocaine 2%) for the Management of Oral Mucositis and Stomatitis: A Phase 3 Prospective Randomized Open Label Multi Centric Parallel Design Study

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ABSTRACT

Background and aim: Oral mucositis occurs in almost 90% of Head and Neck cancer patients receiving radiotherapy. Zinc L carnosine, the chelation of zinc with carnosine, is beneficial for oral mucosal ulcers due to its antioxidant properties. It also causes increased mucous production, which helps repair the injury. The pain in oral mucositis can be addressed with the help of a local anesthetic agent, lignocaine hydrochloride. The objective was to study the efficacy of ZINOBLISS (Zinc Carnosine 2% and lignocaine HCl 2%) for managing oral mucositis and stomatitis.

Material and methods: It was an open-label, multicentric, parallel-group interventional clinical trial. The total number of patients included in the study was 45 (each group was 15). Arm 1 included topical administration of Zinobliss (Zinc Carnosine 2% and Lignocaine HCl 2% Gel) thrice daily for ten days or until healing, whichever was earlier. Similarly, Arm 2 and Arm 3 included topical administration of Hexigel (Chlorhexidine Gluconate Gel) and Zytee- L (Gel containing Choline Salicylate, Lignocaine Hydrochloride, and Benzalkonium Chloride solution), respectively, thrice daily for ten days or until healing whichever was earlier.

Results: The accelerated healing response in subjects treated with Zinobliss by day 4, compared to Hexigel and Zytee L, took 7 to 10 days. Zinobliss treatment did not necessitate any modifications to the subject's diet plans.

Conclusions: Zinobliss is a highly effective and well-tolerated treatment option for oral mucositis and stomatitis.

1. Introduction

Oral mucositis is the inflammatory response occurring in the mucosa of the oral cavity to any noxious agent, mainly the antineoplastic treatment.[1, 2] It is painful and causes odynophagia, dysgeusia, malnutrition, and dehydration.[3, 4] Oral mucositis is graded from grade 1 to grade 5 ranging, from mucosal erythema, patchy ulcer, confluent ulcer, minor trauma leading to bleeding, mucosal necrosis with spontaneous bleeding, and finally death.[5] This oral mucositis can affect the hospital stay, prognosis, and treatment plan. Oral mucositis occurs in almost 100% of patients with Head and Neck cancer receiving radiotherapy.[5] Hence, this adverse reaction caused by anticancer treatment warrants more specific management. With better management, we can reduce the extra burden both Healthwise and financially. Zinc L carnosine, chelation of zinc with carnosine is beneficial for the oral mucosal ulcer due to its antioxidant properties.[4] It also causes increased mucous production, which helps repair the injury. The mucosal adhesiveness provided by Zinc L carnosine heals the ulcer rapidly. Zinc found in tofu, meat, and shellfish is needed for wound healing (skin, connective tissue, and gastrointestinal lining). Carnosine (dipeptide) is formed from beta-alanine and L-histidine. It involves various physiological functions, including anti-inflammatory, antioxidant, and immunomodulatory.[6, 7] These properties can reduce epithelial inflammation and hasten the recovery of oral mucositis and

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stomatitis. The pain in oral mucositis can be addressed with the help of a local anesthetic agent, lignocaine hydrochloride.[8] It blocks the voltage-gated sodium channel, interfering with the nerve signal(pain). By combining lignocaine hydrochloride with zinc L carnosine, the inflammation and ulcer of oral mucosa can be healed faster. Drugs like benzydamine, chlorhexidine, GM-CSF, and Palifermin were used to treat oral mucositis.[9, 10] Many other drugs were also tried to restore the mucosal integrity. These drugs achieve the heal of ulcers by causing proliferation(epithelial), migration, and differentiation. This study focused on the efficacy and safety profile of Zinc L carnosine combined with Lignocaine hydrochloride. The objectives of this study were;

1. To study the efficacy of ZINOBLISS (Zinc Carnosine 2% and lignocaine HCl 2%) for managing oral mucositis and stomatitis.

2. To compare the efficacy of Zinobliss with Hexigel (Chlorhexidine Gluconate Gel) and Zytee-L (Choline salicylate, Lignocaine Hydrochloride and Benzalkonium Chloride Solution)

3. To assess the safety and tolerability of ZINOBLISS (Zinc Carnosine 2% and lignocaine HCl 2%) for managing oral mucositis and stomatitis.

2. Material and methods

It was an open-label, multicentric, parallel-group interventional clinical trial, where 45 participants, male or non-pregnant female subjects whose age was greater than 18 years, diagnosed with oral mucositis and stomatitis were randomized into 3 groups with 15 subjects in each group. Arm 1 included topical administration of Zinobliss (Zinc Carnosine 2% and Lignocaine HCl 2% Gel) thrice daily for 10 days or until healing, whichever was earlier. Similarly, Arm 2 and Arm 3 included topical administration of Hexigel (Chlorhexidine Gluconate Gel) and Zytee- L (Gel containing Choline Salicylate, Lignocaine Hydrochloride, and Benzalkonium Chloride solution) respectively, thrice daily for 10 days or until healing whichever was earlier. The IEC approved and registered the study in CTRI (REF/2023/01/063041).

Study participants

The study included 45 study participants diagnosed with oral mucositis and stomatitis. Screening procedures included demographic data (height, weight, Body Mass Index [BMI] and age), medical and medication history, physical examination, clinical laboratory tests [hematology (CBC) & biochemistry (RBS) with examination of the oral lesion and measurement of the same with photographs. Male or female patients greater than 18 years of age diagnosed with oral mucositis, stomatitis, lichen planus, submucosal fibrosis, erythroleukoplakia, mouth ulcer due to nutritional deficiency or after radiotherapy were included in the study. Those with a history of known allergic reactions attributed to compounds of similar chemical composition to zinc lignocaine, triamcinolone, chlorhexidine, or other chemotherapy drugs were excluded from the study. Patients with cardiovascular, pulmonary, hepatic, renal, haematological, gastrointestinal, endocrinal, immunologic, dermatologic, neurological, or psychiatric disease and a known history of HIV infection or active hepatitis B or hepatitis C infection were also excluded from the study. During the study (24 hours before subject admission to the study site and throughout the study period), participants were restricted from alcohol and smoking.

Ethical consideration

The scientific committee and the Independent Ethics Committee (Institutional Human Ethics Committee) approved this study, which reviewed the protocol and informed consent form. The patients were informed about the study procedure and obtained their consent. The Declaration of Helsinki carried out this research. The subjects were evaluated for the following parameters:

1. Reduction of oral and pharyngeal pain before and 60 min. After administration of test drugs, they are measured on a Visual Analogue Scale (VAS). [Time frame: 10 days].

2. Healing of Mucositis/ stomatitis (assessed by investigator- with pictures) [time frame: 10 days]

3. Incidence and duration of treatment-emergent xerostomia. [Time frame: 10 days]

4. Incidence and duration of taste disturbance, oral irritation / burning sensation, and tooth staining. [Time frame: 10 days]

5. Use of rescue medication (analgesics) for pain. [Time frame: 10 days]

6. Incidence of need for a modified diet (soft, liquid, TPN) [Time Frame: 10 days].

Safety and tolerability of the study drug were evaluated by Clinical AEs, including laboratory abnormalities (If any) by the following:

1. Impact of the treatment on activities of daily living [Time Frame: 10 days] via a validated Oral Mucositis Daily Questionnaire (OMDQ)

2. Proportion of patients having a confirmed best response, partial response, or complete response. (10 days duration)

3. The quality of life among the study participants were assessed using pre and post Study questionnaire (SF 12)

4. Adverse events and serious adverse events during the study period.

Statistical analysis

Descriptive statistics were given for baseline characteristics like age, sex, and any adverse events and tolerability profiles. All the results were evaluated and compared between the test and comparator groups using ANOVA and T-test by SPSS software version 21.0. Independent T-test analyzed scores and survey results of different patients. $P<0.05$ is considered significant.

3. Results

Demographic details

The study included 45 subjects with mucositis and stomatitis in the age group of 18 and above divided into three groups with predominantly female subjects. 50% of subjects belonged to the age group of 18-30 years. About BMI distribution, 50% of patients were in the normal range. (Tables 1-3).

Table 1. Age-wise distribution.

Age in Years	Groups			Total
	Hexigel N (%)	Zinobliss N (%)	Zytee-L N (%)	
18-30	8 (37.78)	8 (34.78)	7 (30.43)	23
31-40	1 (25)	1 (25)	2 (50)	4
41-50	4 (57.14)	2 (28.57)	1 (14.29)	7
51-70	2 (18.18)	4 (36.36)	5 (45.45)	11
Total	15	15	15	45

Table 2. BMI-wise distribution.

BMI	Groups			Total
	Hexigel N (%)	Zinobliss N (%)	Zytee-L N (%)	
Underweight	1 (50)	1 (50)	0	2
Normal	9 (39.13)	5 (21.74)	9 (39.13)	23
Overweight	3 (30)	4 (40)	3 (30)	10
Obesity	2 (20)	5 (50)	3 (30)	10
Total	15	15	15	45

Table No: 3 Gender-wise distribution

Gender	Groups			Total
	Hexigel N (%)	Zinobliss N (%)	Zytee-L N (%)	
Male	3 (20)	4 (26.67)	8 (53.33)	15
Female	12 (40)	11 (36.67)	7 (23.33)	30
Total	15	15	15	45

There is a significant improvement (earlier healing) in the Zinobliss group in around 4.9 days, compared to the other groups with more than 6 days. Faster healing was observed with Zinobliss treatment. There was a significant improvement (earlier healing) in the Zinobliss group compared to the other groups. On applying ANOVA, there was a significant difference between the groups (0.0028). (Fig. 1)

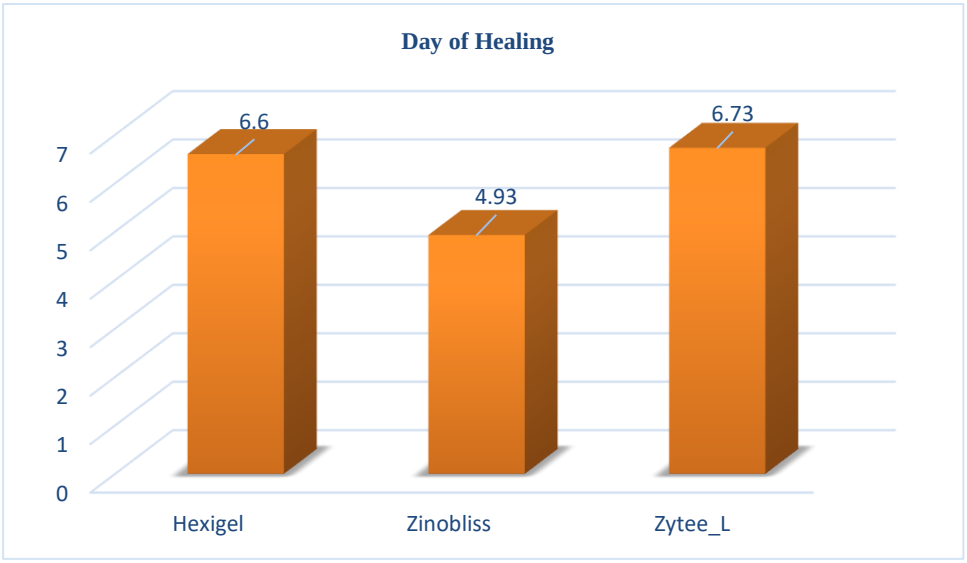


Fig. 1. Comparison of Day of Healing.

There is a significant reduction in all three groups concerning the Pain VAS scores from baseline to 1 hour after application and post-study. However, there is a significant reduction in Pain(quantitatively) in the Zinobliss group after 1 hour of application compared to the other two groups. On applying Repeated Measure ANOVA, there was a significant difference in pain score (pre and post-study). P-value 0.0001. (Fig. 2)

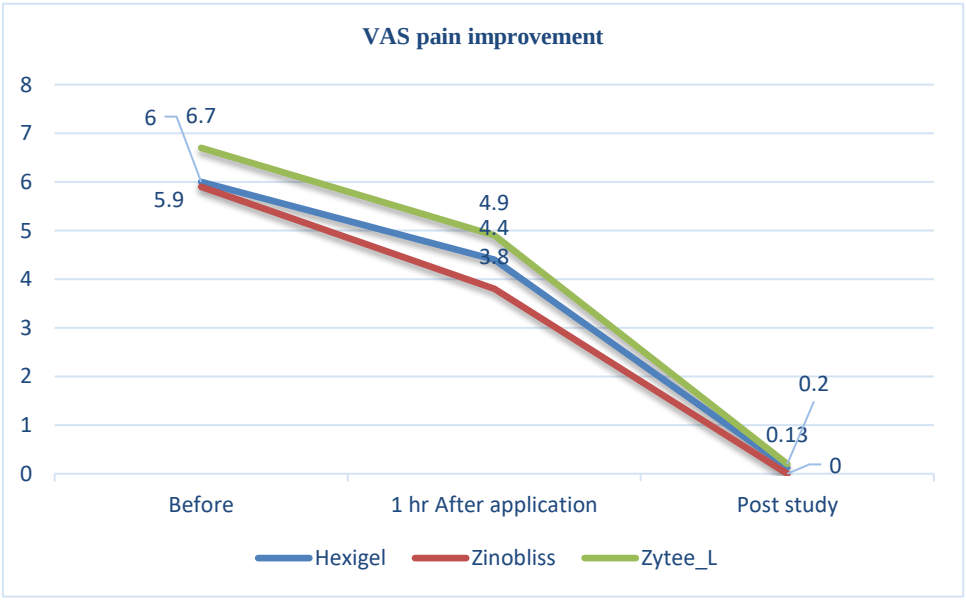


Fig. 2. PAIN- VAS Score comparison.

There was a significant improvement (healing) in the lesion size by day 4 in the Zinobliss treatment group compared to the other two groups. Day 4 of treatment showed reduced lesion size in the zinobliss group with a P-value of 0.004 compared to the other two groups. (Fig. 3)

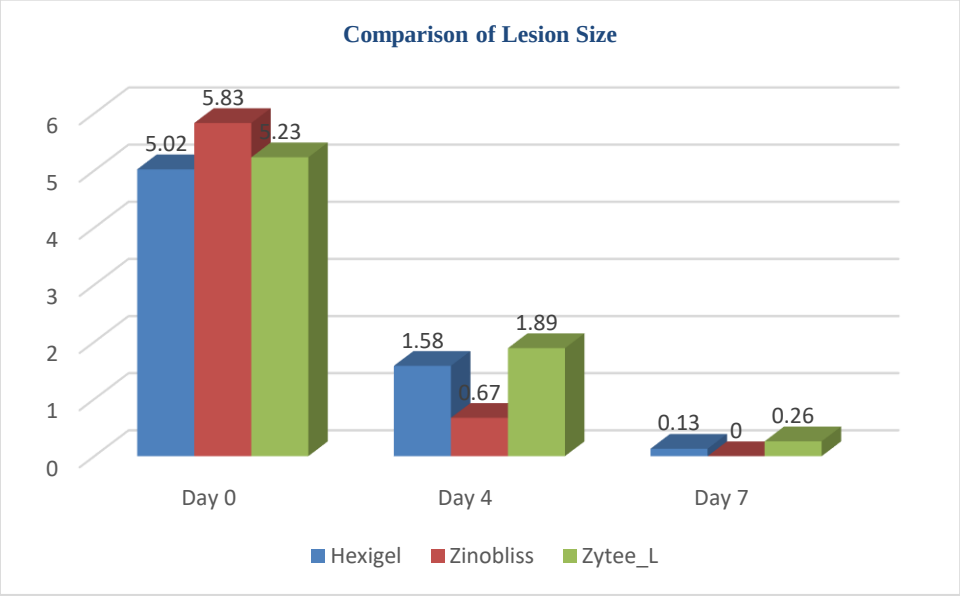
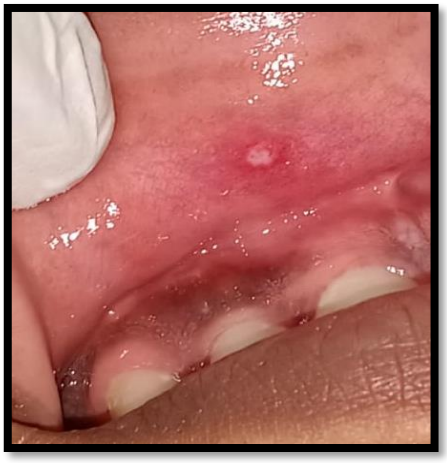
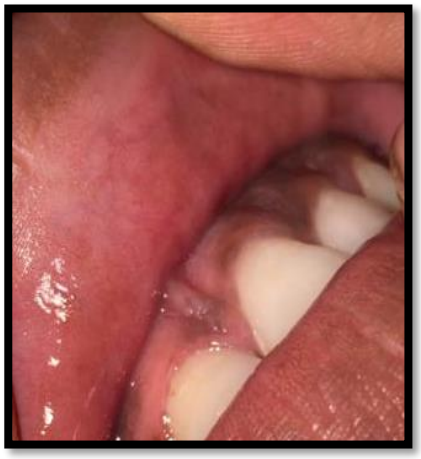
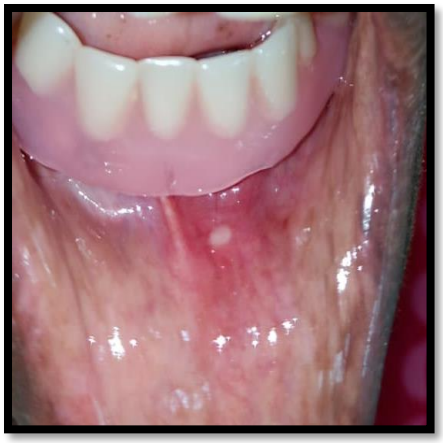
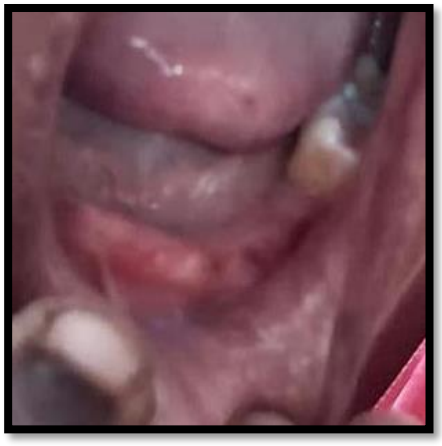


Fig. 3. Comparison of lesion size.

Drug	Before	After	Day of Healed
Zytee-L			8
Hexigel			9

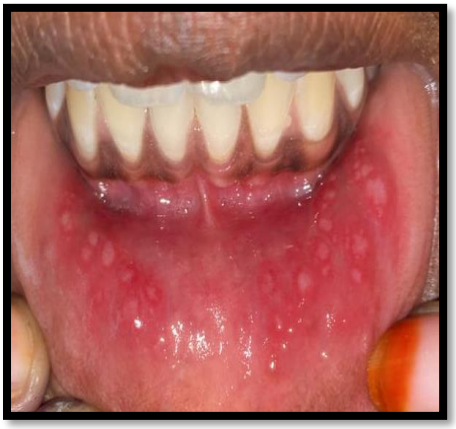
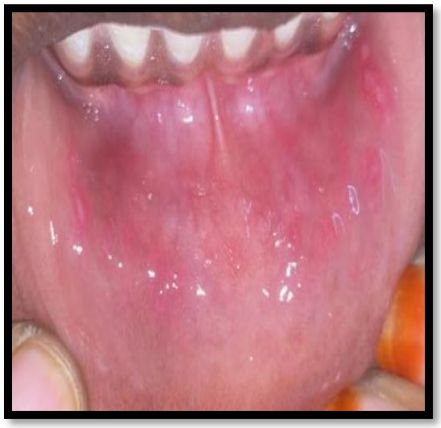
Zinobliss			5

Fig. 4. The gross image of oral mucositis (before and after application of treatment drugs) in Zytee-L, Hexigel, and Zinobliss group.

4. Discussion

In this design study, we evaluated the efficacy and safety of Zinobliss. We found that the number of days of healing was decreased in the Zinobliss group compared with the other two groups. The combination of zinc carnosine with lignocaine hydrochloride has restored mucosal integrity at a faster rate than a single drug. Oral mucositis was completely healed in fewer days in the Zinobliss group compared to the other two treatment groups, which was statistically significant. Regarding the demographic details, Patients between 18 and 30 years were in all three groups. Based on the body mass index, more participants in all three groups had a normal range of BMI. The mean day of healing in the zinobliss group was 4.93(Fig. 1), which was significantly less in number with a p-value of 0.0028 compared to Hexigel and Zytee-L. Complete healing in the Hexigel and Zytee-L group took 7 to 10 days. The mean size of oral mucositis was 5 mm in all three treatment groups. On day 4 of treatment, the zinobliss group showed reduced lesion size (less than 1 mm) compared to Hexigel and Zytee-L. By day 7, the lesion had fully disappeared in the Zinobliss group. Healing of ulcer wounds in the zinobliss group can be explained by the action of ZincZinc, which causes re-epithelialization, a vital step in the wound healing process.[11-13] ZincZinc also controls the oxidative stress of the cells. Tripartite motif family (TRIM) proteins play a role in wound repair. Mitsugumin 53 (MG53), or TRIM 72, helps repair the cell membrane. The binding of ZincZinc is required for this repair mechanism to occur.

Pain due to the ulcer was assessed with the help of the Visual Analogue Scale, where participants in the zinobliss group showed significantly lesser VAS scores during 1-hour post-application of the drug when compared with the other two groups (Hexigel and Zytee-L). (Fig. 2). There was a rapid onset of action in Zinobliss (Zinc Carnosine 2% and Lignocaine HCl 2%) treated subjects by eliciting a reduction in Pain score after 1 hour of application, compared to the other two groups. This can be attributed to the local anesthetic agent lignocaine hydrochloride. It reduces the signal transmission of pain impulses by blocking the voltage-gated sodium channel.

Additionally, Zinobliss treatment did not necessitate modifying the subject's diet plans. This aspect is particularly significant in oral healthcare, where dietary restrictions can impact an individual nutritional intake and overall well-being. The quality of life was assessed by a short questionnaire, where day-to-day activities, peaceful and calm mind, energy level, and social activities like visiting friends were listed. There was no significant difference among the three treatment groups. Thus, ZINOBLISS, a Novel combination of Zinc Carnosine 2% and lignocaine HCl 2% has a better health benefit in treating patients with Oral Mucositis and stomatitis when compared to Hexigel (Chlorhexidine Gluconate Gel) and Zytee-L (Choline salicylate, Lignocaine, Hydrochloride and Benzalkonium Chloride Solution). In a study done by Mehdipour et al.,[14] zinc sulphate and chlorhexidine gluconate mouthwash were compared in preventing chemotherapy-induced oral mucositis, 15 patients who had received Zinc sulphate mouthwash developed only less severe mucositis, whereas in patients who used chlorhexidine mouthwash developed highly severe mucositis. It showed that ZincZinc is more efficacious in preventing mucositis than chlorhexidine.

Similarly, our study also exhibited faster healing of oral mucositis by Zinobliss (Zinc L Carnosine and Lignocaine Hydrochloride) compared to Hexigel (Chlorhexidine gluconate gel). A study by Mosalaei et al.[15] was a phase 3 placebo-controlled trial, where patients who received Zinc sulphate 200 mg oral tablet thrice daily during radiotherapy demonstrated the effectiveness of ZincZinc in reducing the severity of oral mucositis. The smaller sample size was found to be the limitation of this study.

5. Conclusion

Our study provides strong evidence that Zinobliss, a novel combination of Zinc Carnosine 2% w/w and Lignocaine HCl 2% w/w gel outperformed Hexigel (Chlorhexidine Gluconate Gel) and Zytee-L (Gel containing Choline Salicylate, Lignocaine Hydrochloride and Benzalkonium Chloride solution) as a highly effective and well-tolerated treatment option for oral mucositis and stomatitis. By holistically treating the condition, Zinobliss provides a valuable tool for healthcare professionals in promoting the overall well-being and quality of life of the patients.

Conflict of Interest

The authors declared that there is no conflict of interest.

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