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Role of Zinc Sulfate in Prevention of Chemotherapy Induced Oral Mucositis

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Abstract:-

BACKGROUND: Chemotherapy has significantly improved survival of cancer patient, but it has many side effects. About 14-81% of patients receiving chemotherapy experiences oral mucositis. Studies have shown zinc supplements may act as protective agent against oral Mucositis. The aim of study was to explore the preventive role of zinc sulfate in chemotherapy induced mucositis.

OBJECTIVES: The objective of the study to evaluate the effectiveness of zinc sulfate in prevention or decreasing severity of chemotherapy induced oral mucositis with chemotherapy regimens having high neutropenic potential.

DESIGN:Open label two arms interventional study, with quantitative study design.

SETTING: Study was conducted at Medical Oncology Department, Fauji Foundation Hospital, Rawalpindi in 6 months duration.

MATERIAL AND METHODS: The patients were enrolled by convenience non-probability sampling technique. They were randomized to interventional arm receiving zinc sulfate plus chemotherapy and no interventional arm receiving only chemotherapy by systematic sampling.

MAIN OUTCOME MEASURES: Incidence and severity of mucositis at day 7 and day 14 in interventional and non interventional arm.

SAMPLE SIZE: It was two arm study with 50 patients in each arm with total of 100 patients.

RESULTS: Chi Square test was applied on the effect of Zinc Sulphate on Mucositis. Mucositis assessed at day 7 & day 14 showed statistically significant difference in Mucositis incidence and severity in number of patients receiving Zinc Sulphate between two arms with p value < 0.00.

CONCLUSION: Zinc Sulphate is an effective adjunct used in our study, which not only showed its effectiveness but also proved to be safe drug without any interactions with chemotherapies. Zinc Sulphate significantly reduced the Mucositis.

LIMITATIONS: This study only evaluated the effect of zinc Sulphate with single cycle of chemotherapy and did not compare the protective effect of zinc sulphate with other preventive agents.

CONFLICT OF INTEREST: None

Keywords:- *Oral mucositis, zinc sulphate, chemotherapy.*

I. INTRODUCTION

Chemotherapy has significantly contributed to the survival of cancer patients, but its side effects remain an importantarea of concern.[1]As chemotherapies act on tumor cells and rapidly proliferatingnormal cells especially the immune cells, capillaries and gastrointestinal tract lining, henceseveral adverse effects occur due to this interaction.[2]The toxicitiesof a chemotherapeutic agent not only depend upon its mechanism of action, dose and interactions, but also on various patients' related parameters like their oral hygiene and genetic factors.[2,3]

Oral mucositis is an important non-hematological side effect of cytotoxic treatments.[4]About 14-81% of patients receiving chemotherapy may experience oral mucositis.[5]With certain medicines it can even be a dose limiting adverse effect.[6] It isassociated with profound pain, thus negatively affecting the patient's nutritional status and quality of life which in turn leads to poor tolerance to therapy. This low tolerance may lead to dose reductions andincreased gaps in therapy. Thus, it not only affects patient's survival but also causes significant economic burden.[7,8,9,10]

Chemotherapy related mucositis usually presents after one week of chemotherapy while the highest number of cases noted are on day 10 post chemotherapy.[7] Oral mucositis

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presents in the form of erythema, swelling and ulceration which predisposes the patient tosystemic and local infections.[11,12]

Pathogenesis of oral mucositis consists of complex series of different microbiological and biological eventsin which different set of cytokines, reactive oxygen species, second messengers and oral flora play an important role in damaging the oral mucosa.[3]Mucositis develops in four steps,in initial inflammatory/vascular phase chemotherapy releases cytokines such as IL-1 and TNF-α which causes tissue damage and increases vascularity.In epithelial phase, chemotherapies which are specific to cell cycle inhibit DNA synthesis in S phase of cell cycle and results in epithelial atrophy,erythema and ulcers. Ulcerative phase is more severe in neutropenic patients, as it causes greater release of inflammatory cytokines and reactive oxygen speciescausing significantdamage. Eventually, the recovery phase requires cell division, their differentiation, recovery of cell counts and bacterial flora suppression.[13]

Chemotherapy regimens including cytarabine, 5-Flourouracil,platinum compoundsand alkylating agents are linked to cause mucositis in literature.[2] Different agents have beentried for prevention of mucositisincluding Chinese herbal medicines, antibiotics, anesthetic agents, anti-inflammatory medicines, chlorhexidine, amifostine, pentoxyfyline, low level laser therapy, cryotherapy, zinc sulfate and non-essential amino acids. However, still there is lack of evidence based standard protocol in this regard.[7,14]Multinational association of supportive care in cancer (MASCC) and International Society of Oral Oncology (ISOO) proposed that in oral cancer, zinc supplements may act as a protective agent against oral mucositis.[14]

Zinc is an essential micronutrient requiredin trace amount and has no internal body storage.[15]Zinc has role in combating inflammation and cell cycle regulation. It acts as a cofactor for DNA synthesis and is important for cell survival and wound healing.Zinc maintains the immune system and its deficiency causes impairment of B cells,T cells,natural killer cells and causes decreased production of T-helper-1 cells.[7,11,16]

There are many scoring systems for assessment of mucositis,most widely used is World Health Organization (WHO) system which is based on clinical picture as well as oral intake of patient.[4]

Literature review showed trials supporting the role of zinc sulfate for prevention ofchemotherapy induced mucositis.[7,9] Conflicting results were shown by some studieswith no significant clinical benefit when used with high dose chemotherapy.No study was found on this topic in Pakistan.

The aim of this studywas to explore the preventive role of zinc sulfate in chemotherapy induced mucositis in our population.

A. Objective:

The objective of this study was:

- To evaluate the effectiveness of zinc sulfate in prevention or decreasing severity of chemotherapy induced oral mucositis with chemotherapy regimens having high neutropenic potential.

B. Operational Definition:

a) Oral Mucositis:
Erythematous and ulcerative lesions of oral mucosa observed in several conditions including chemotherapy.[17]

b) Incidence of Oral Mucositis:
New cases of oral mucositis irrespective of grade divided by the total number of cancer patients completed the whole study.[10]

c) WHO grade of Mucositis:[7]

Grade	Changes
0	No subjective or objective changes of mucositis
I	Oral soreness and erythema in mucosa, gums tongue or palate
II	Erythema and ulcers,but solid diet tolerated
III	Erythema and oral ulcers, only “pasty” food and liquid tolerated
IV	Erythema and ulcers and pain,inability to swallow liquids,oral alimentation impossible, narcotics for pain relief.

Table 1: WHO grades of mucositis

II. MATERIALS AND METHODS

A. Setting:

After approval from ethical review committeeof ourhospital, the study was conducted at Medical Oncology Department, Fauji Foundation Hospital, Rawalpindi.

B. Study design:

Open label two arms interventional study, with quantitative study design.

C. Duration of study:

6 months starting from date of approval.

D. Sample size:

It was two arm study with 50 patients in each arm. After taking informed consent, a total of 100 patients were enrolled.Sample size was calculated with WHO sample size calculator 1.1.[7]

E. Sampling Techniques:

Two step sampling technique was used. First, the patients wereenrolled by convenience non-probability sampling technique. Then they wererandomized to interventional arm

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receiving zinc sulfate plus chemotherapy and no interventional armreceiving only chemotherapy by systematic sampling by allotting all patients reporting on odd numbers to interventional arm and even numbers to non-interventional arm.

III. SAMPLE SELECTION

A. Inclusion Criteria:

- Patient aged ≥ 12 years
- Conscious and oriented patients
- No evidence of mucositis prior to chemotherapy
- Patients receiving chemotherapeutic regimens withneutropenic potential of >20%.[18]

B. Exclusion Criteria:

- Prior radiotherapy to head & neck region
- Pregnancy and lactation
- Patients allergic to zinc compounds.
- Patients with conditions predisposing to oral mucositis like Sjogren's syndrome.

IV. CONCEPTUAL FRAMEWORK OF THE STUDY

- Open label two arms interventional study with quantitative study design

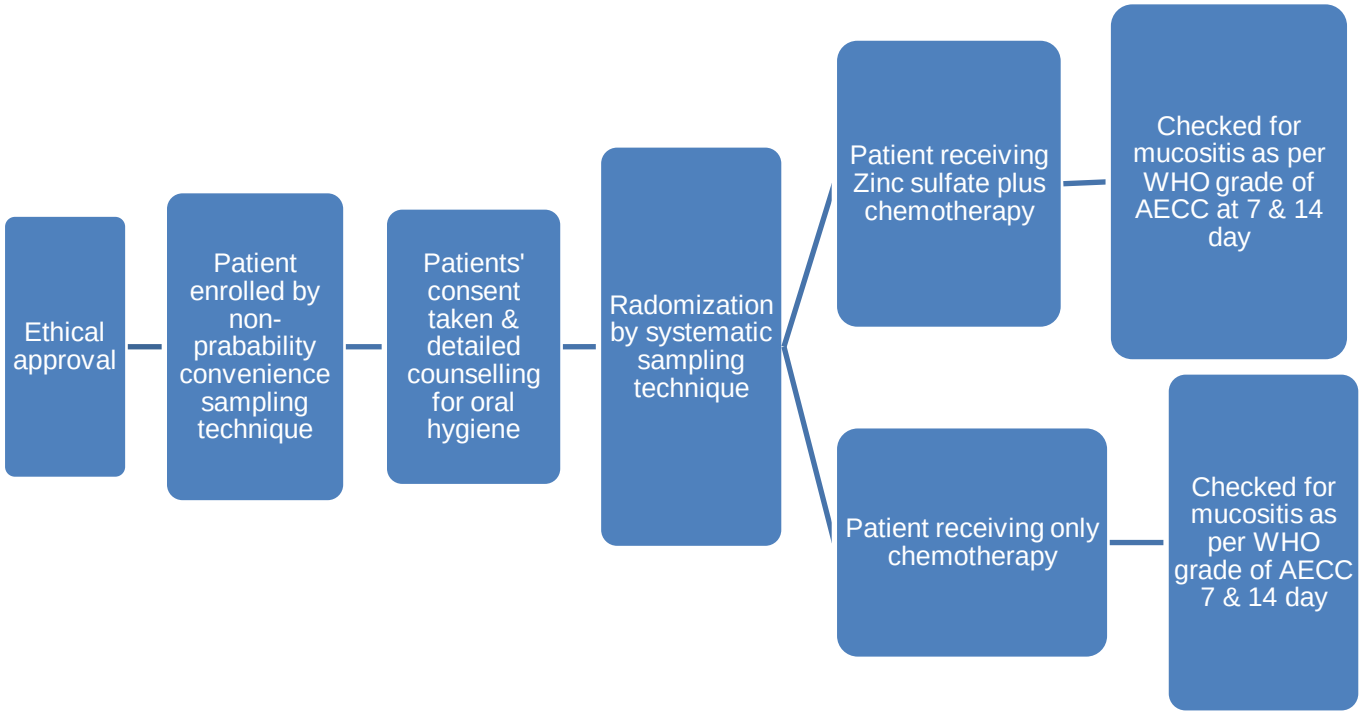

Fig. 1: Conceptual framework of study

V. DATA COLLECTION

Patient fulfilling the inclusion criteria were enrolled in the study.Patients receiving chemotherapy with high neutropenic potential (>20%) without any baseline mucositis were enrolled in the study by non-probabilityconvenience sampling technique. After taking an informed consent for participation in the study, patients were randomized into two arms by systematic sampling technique. Randomization of all patientswas done by giving odd serial numbers to interventional arm andeven numbers to non-interventional arm. Atotal of 50 patients were enrolled in each arm. Interventional armreceived zinc sulfate syrup plus chemotherapy while the other arm received chemotherapy alone.The zinc sulfate syrup was prescribed for 14days as thrice aday dosage schedule.Patients were counseledon oral hygiene including soft tooth brush,avoidance of tobacco and alcohol etc.Objective assessment of mucositis was accessed by oral toxicity scale of World Health Organization.Mucositis was accessed on7 and day 14 post chemotherapy for incidence as well as severity.

VI. RESULTS

In this study a total of 100 patients were enrolled in two arms; intervention arm (Zinc Sulphate supplementation n=50) and control arm (n=50). Overall, the mean age of patients was 48.33 ± 12.2. SPSS version 23 was used to analyze data.Various histological diagnoses were included and the commonest diagnosis was breast cancer (87 patients, 87%), followed by ALL (8 patients,8%)and lymphoma (NHL and Hodgkin lymphoma) as shown in table 2. Majority of patients were given dose dense AC→Paclitaxel regimen (87%), followed by HyperCVAD regimen and DHAP.

ISSN No:-2456-2165

Descriptive statistics are given as percentages and frequency of all these qualitative variables (histologies and chemotherapy regimens)in table 2.

	n (%)
Diagnosis	
CA Breast	87 (87%)
ALL	8 (8%)
NHL	3 (3%)
Hodgkin's lymphoma	2 (2%)
Chemotherapy	
AC→PACLI	87 (87%)
HyperCVAD	8 (8%)
DHAP	5 (5%)
Zinc Sulphate intervention	
Done	50 (50%)
Not done	50 (50%)

Table 2: Overall baseline characteristics of patients (n=100)

As part of analytical statistics, Chi square test was applied to identify statistical significance of any reduction in severity of mucositis in Zinc Sulphate arm. A *p* value of ≤0.05 was considered significant. This analysis showed thatmucositis assessed at day 7 showed statistically significant difference in mucositis incidence as well as severity in patients receiving Zinc Sulphatewith a p value < 0.00 and Pearson chi square value was 40.108.

	Value	**Df**	**Asymp. sig. (2-sided)**
Pearson chi-square	40.108	3	.000
Likelihood ratio	48.315	3	.000
Linear-by-linear association	37.637	1	.000
N of valid cases	100		

Table 3: Chi square test for mucositis at day 7

Only 9 patient (18%) developedgrade 1 mucositis at day 7 in intervention arm as opposed to 21(42%) patients in non-interventionarm, while none of the patient had grade 2 or grade 3 mucositis in intervention arm. Thus,the incidence as well as the severity of mucositis was markedly reduced with the co-administration of ZnSO4, when assessed at day 7 in patients receiving various chemotherapies in our study, as shown in figure 2.

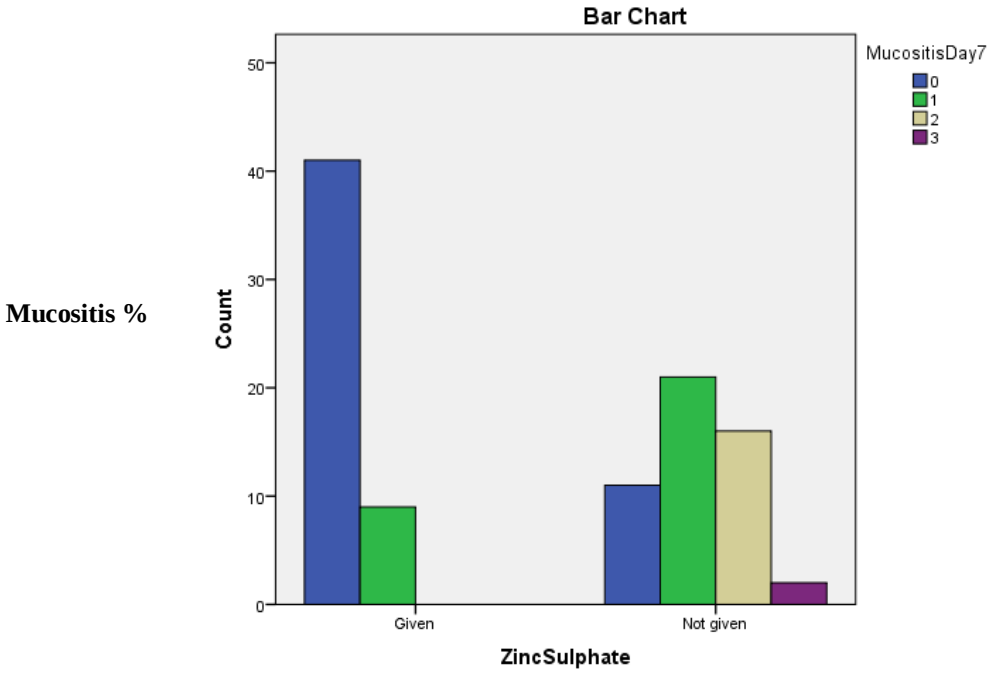

Fig. 2: Bar chart showing relationship between grades of mucositis in intervention & non- intervention arm at day 7

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For the Assessment for mucositison day 14, chi square test was applied and Pearson chi square value was 42.949, confirming positive affect of intervention on incidence at day 14 as well. At day 14 also, among intervention arm, only 4 patients (8%) developed grade 1 mucositis as compared to 30 patients (60%) in non-intervention arm. Neither Grade 2, nor grade 3mucositis was observed in intervention arm in comparison to non-intervention cohort where 6 patients developed grade 2 mucositis. Thus, the total incidence of mucositis was72% in non-intervention arm as compared to 8% in intervention arm, with ap valueof less than 0.00, confirming its statistical significance as well.

	Value	Df	Asymp. sig. (2-sided0
Pearson chi-square	42.949	2	.000
Likelihood ratio	48.806	2	.000
Linear-by-linear association	38.805	1	.000
N of valid cases	100		

Table 4: Chi square test for mucositis at day 14

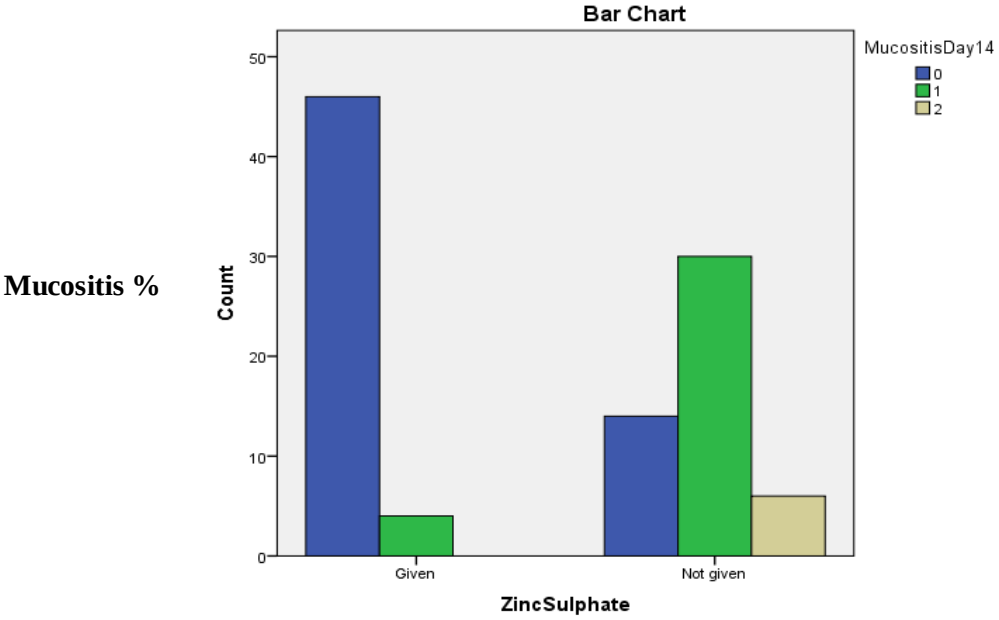

Fig. 3: Bar chart showing relationship between grades of mucositis in intervention & non- intervention arm at day 14

VII. DISCUSSION

Chemotherapy is an important modality in the armamentarium against various malignancies. It has good cure rates but there are various hinderances in its use including cost, chemotherapy phobia, side effects and post chemotherapy care required at home.One of the commonest factors affecting compliance of chemotherapy is side effects of the treatment that the patients experience.[1]These side effects are haematological as well as non-haematological affecting several organs of the body. Oral mucositis is a non-hematological side effect of chemotherapy and about 14-81% patients experience this side effect.[4,5] Thus, negatively affecting patients' nutrition and leading to poor tolerance,dose reductions and gaps in chemotherapy which affects survival of the patients and causes economic burden as well.[7,8,9,10]. Different agents have been tried for prevention of mucositis including Chinese herbal medicines, antibiotics, anesthetics, anti-inflammatory agents,laser therapy, cryotherapy, zinc sulphate and non-essential amino acids. However, still there is lack of evidence based standard protocols for the prevention of chemotherapy related mucositis.[7,14]

We used Google scholar and pub med for literature search regarding the zinc sulphate and oral mucositis. Zinc sulphate has been reported in literature to have some protective effect against chemotherapy induced mucositis.[7,9,19] Zinc sulphate is believed to have protective role by combating inflammation, acting as a cofactor for DNA synthesis and maintaining immune system.[7,11,16] But there is no clear evidence as conflicting results are shown by some studies, where no significant benefit is shown with high dose chemotherapies esp. the pre-transplant conditioning regimens.[20]Moreover, no local study is available to study this dimension of mucositis. Hence, it is an important area to explore if mucositis can be prevented or minimized to improve outcome of patients receiving various chemotherapies. With this background we studied the effect of zinc sulphate in prevention or decreasing the severity of chemotherapy induced oral mucositis in our population.

Rambod et al studied effect of zinc sulphate on prevention and reduction in severity of mucositis in adult patients treated for leukemia.[7] We included solid and hematological malignancies who were treated with chemotherapy with high neutropenic potential > 20%. Their Mean age in the intervention arm was 39.17 ±17.07 years and

33.80±13.73 years in non-intervention arm.[7] In our study, mean age in experimental group was 47.5 year ± 12.97 years and in non-experimental group it was 49.14 ±11.5. They showed a reduction in the incidence of mucositis by 75% in investigational arm and it was found to be 47.7% in control arm in their study.[7]While,in our study, 82% patient didn't experience mucositis in investigational arm as compared to 22% in non-investigational arm on day 7. This rate was 92% reduction as compared to 28% in non-experimental arm when assessed on day 14. Regarding the severity of mucositis, there was a marked difference between the two cohorts concerning the mean score of severity of mucositis with p value = 0.01.[7] Our study showed significant reduction as well both on day 7 and day 14 in severity of mucositis with p value < 0.00.

Mansouri et al studied effect of zinc sulphate on prevention of mucositis in patient receiving conditioning regimen for hematopoietic stem cell transplant (HSCT). Their study failed to show significant protective effect with p value of 0.748.[20]Their study population was all leukemia patients receiving conditioning regimen. In contrast to their study, our patients were mix of solid (92%) and hematological malignancies (8%). This could be the reason of conflicting results between our studies. Their study population was younger as compared to our study and their mean age in intervention arm was 30.87 years as compared to 47.5 years. In subset analysis we have 8 patients of ALL received HyperCVAD chemotherapy regimen. Our study proved improved outcome with Zinc sulphate and showed statistically significant results with p value of 0.018.Their chemotherapy regimens were aggressive conditioning regimens as compared to our regimens which could be the main underlying factor in the difference of results.

While we had some encouraging results, our study had some limitations as well. We took patients from different malignancies with different chemotherapy protocols. Next study can include single malignancy with same regimen so that effect on that cancer can be studied without any bias.Cohorts were not match with respect to chemotherapy regimen and dosage. We only studied the effect of zinc Sulphate with single cycle of chemotherapy. We did not compare the protective effect of zinc sulphate with other preventive agents so in future more extensive multicentric randomized controlled studies are needed which can evaluate its protective effect on different malignancies and be able to compare it with other agents.

Still our study has practical implication, as we can easily administer zinc sulphate with different chemotherapy regimens having high neutropenic potential. Moreover, zinc sulphate is easily available, cost effective, has shown no interactions with chemotherapy and easy to administer which will protect the patient from oral mucositis thus improving nutritional status,minimizing chemotherapy breaks, better chemotherapy response and hence improved patients' outcome.

VIII. CONCLUSION

Zinc Sulphate is an effective adjunct used in our study, which not only showed its effectiveness by reducing both the incidence as well as severity of mucositis in our patients. Also,it proved to be a safe drug without any interactions with chemotherapies. The significant reduction of mucositis by Zinc Sulphatetranslated into improved patients' compliance and better tolerance of chemotherapy, resulting in expected improved outcomes.

We recommend further studies to study the effectiveness of zinc sulphate and imply this useful drug in prevention of this challenging side effect of chemotherapies.

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