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Research Article

TIME BOUND EVALUATION OF ROLE OF SERUM ZINC LEVEL IN CLINICAL TYPES OF ORAL LICHEN PLANUS AND ITS CO-RELATION WITH ASSOCIATED SIGN AND SYMPTOMS

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A B S T R A C T

Aims and objectives: The present study aims at evaluation of serum Zn level in study case and controls. The co-relation between serum Zn level and Numerical rating Scale, change in symptoms, modified oral mucositis index in patients with Zn and without Zn has been also assessed by this study.

Materials and Methods: A total of 30 patients with erosive lichen planus , non erosive lichen planus and 30 healthy individuals as the control group were recruited in this study. In a patient with clinically and histopathologically confirmed case of oral lichen planus 20mg Zinc (in form of'zinconia' tablets) is given once a daily from baseline(0 day), 15 days, 30 days and 45 days. The 5ml bloodfrom each patient is collected at baseline (0 day), 15 days, 30 days and 45 days by venipuncture. The serum Zn level is analysed by Inductively Couple Plasma **(**ICP) protocol at baseline (0 day), 15 days, 30 days and 45 days.

Results: The serum Zinc level after Zinconia Tab (20 mg) administration once a day at 15 day, 30 days and 45 days are statistically significant($P<<0.001$*) to serum Zinc level at base line i.e. as the time of treatment with Zinconia tab increases, the serum level of Zinc increases. The mean serum Zinc level in male and female subjects of study population was statistically non-significant ($P<.05$) at baseline 0 Days,15 days,30 days,45 days. serum Zinc level at baseline(0 day),15 day,30 day,45 days was statistically non significant($p<.05$) i.e after administration of 20 mg Zinconia tab OD in all age group the serum zinc level has no significant difference.

Conclusion: As duration of zinc intake increases, the mean serum zinc level increases and symptoms of pain (NRS) decreases or vice versa in lichen planus. The serum zinc level affects the change in symptoms scale (CSS). The mean serum Zinc level does not affect the degree of erythema in oral lichen planus patients. As the mean serum Zinc level increases from base line (0 day) to 45th day of treatment, the ulceration in study subjects reduces in size and intensity.

INTRODUCTION

Lichen planus is a chronic, autoimmune [1,2] disease that can affect the skin as well as the mucous membranes[3]. It can appear clinically as white reticular keratotic changes, erythematous changes, and erosions[4] on involving the oral mucosa. Oral lichen planus can occur on any mucosal surface, including the lips, but most frequently occurs on the buccal mucosa. Symptoms can range from none, with the patient being unaware of the intraoral lesions, to extremely painful lesions that may interfere greatly with eating, and thus significantly affect quality of life. Many underlying factors are related to or associated with the process of this disease[5,6].

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Some of these factors include the disturbance in the body immune system and the role of cytotoxic T-lymphocytes and monocytes, as the main constituent in the pathogenesis of the disease[5]. Several factors can influence T-lymphocytes such as stress, diabetes, hepatitis C, trauma, drugs and metal sensitivity[6]. Trace elements, such as zinc and copper, are precisely involved in metabolic processes that are critical for cell differentiation and replication. Alterations in the level of these elements are considered as a part of defense strategies of organisms which is crucial for stability of cell membrane, apoptosis, host metabolism and enzyme activities[7].

Zinc is one of the most essential elements in growth and development of epithelium; moreover, it is a requisite element for cellular function and metabolism of carbohydrates, proteins and lipids[7,8]. The role of zinc in modulating oxidative stress has recently been recognized. Oxidative stress is an important contributing factor in several chronic human diseases, such as atherosclerosis and related vascular diseases, mutagenesis and

cancer, neurodegeneration, immunologic disorders like lichen planus, and the aging process[9-11] Together O , H O , and .OH are known as reactive oxygen species (ROS), and these are produced continuously *in vivo* under aerobic conditions. The NADPH oxidases are a group of plasma membrane associated enzymes, which catalyze the production of O from oxygen by using NADPH as the electron donor. Zinc is an inhibitor of this enzyme. The dismutation of O to H O is catalyzed by an enzyme super oxide dismutase (SOD), which contains both copper and zinc. Zinc is known to induce the production of metallothionein, which is very rich in cysteine, and is an excellent scavenger of .OH[12]. Iron and copper ions actuate the production of .OH from H O. Zinc is known to compete with both iron and copper for binding to cell membrane, thus decreasing the production of .OH[12].

In india there is a scarcity of studies and researches regarding role of zinc element in lichen planus. Therefore, the present study aims to evaluate the levels of serum zinc in erosive and non erosive oral lichen planus and compares it with healthy group to find out any believable inference.

MATERIALS AND METHOD

The present study has been conducted from May 2017 to May 2018**.** A total of 30 patients with erosive lichen planus and non erosive lichen planus and 30 healthy individuals as the control group were recruited in this study. All participants were selected from the Department of Oral Medicine and Radiology, King George's Medical University, Lucknow. 18-60 years old Subjects having clinically and histopathologically diagnosed oral lichen planus were included in the study. The patients having any factor related to lichenoid reaction such as amalgam fillings near the lesion, consumption of medication which are associated with lichenoid reaction, Patients whose histopathological findings shows dysplastic changes, Consumptions of drugs other than zinconia that would influence the level of serum zinc level, Patient not interested in the study, Patients with malabsorption problem, Presence of other factors that would affect the absorption of zinc like intake of calcium, iron supplements, pregnancy etc, Patients consuming alcohol were excluded from study.

In a patient with clinically and histopathologically confirmed case of oral lichen planus 20mg Zinc (in form of'zinconia' tablets) is given once a daily from baseline(0 day), 15 days, 30 days and 45 days. The 5ml bloodfrom each patient is collected at baseline (0 day), 15 days, 30 days and 45 days by venipuncture. The serum Zn level is analysed by Inductively Couple Plasma **(**ICP) protocolat baseline (0 day), 15 days, 30 days and 45 days. The serum was diluted with Mili-Q water in a ratio of 1:3. The resultant clear solution was then analysed by Inductively Couple Plasma-Optical Emission Spectrometer (ICP-OES) (Optima 8000, Perkin Elmer, USA).

Operating Conditions	Value
Plasma Gas Flow (L/min)	8
Auxiliary Gas Flow (L/min)	0.2
Carrier Gas Flow (L/min)	0.55
RF Power [W]	1300
Plasma view	Axial
Sample flow rate (ml/min)	1.5

The values of Zn serum level will be recorded in structured Performa for the same. SPSS 21v version will be used for data analysis.

RESULTS

The study population consists of 30 study subjects with mean age 37.56+12.90 (Table.1).

Table 1 Showing the minimum and maximum age in study population

	N	Minimum	Maximum	Mean	Std. Deviation
Age	30	20.00	72.00	37.5667	12.90197

The male subjects (53.3%) dominates the study population than females (46.7 %) (Table.2).

Table 2 Showing the frequency of male and female in study population

Gender	N	Percent
Male	16	53.3
Female	14	46.7
Total	30	100.0

The study population is divided in 3 age groups. The maximum study subjects 20 (66.7%) were age group 20-40 years followed by 9 (30%) in age group 41-60 however > 60 years age groups contains 1 study subjects (Table.3).

Table 3 Showing the age group wise distribution of study population

Age intervals	N	Percent
20 to 40 years	20	66.7
41 to 60 years	9	30.0
Above 60 years	1	3.3
Total	30	100.0

In the study population (30), the serum Zn level at baseline (0 day) is compared with serum Zn level at 15 days by paired t-test of significance and it was found that the mean serum Zn level was statistically significant (P<0.001*) after 15 days of treatment. The serum Zn level at baseline (0 day) is also compared with serum Zn level at 30 days by paired t-test of significance and it was found that the mean serum Zn level was statistically significant (P<0.001*) after 30 days of treatment. The serum Zn level at baseline (0 day) is also compared with serum Zn level at 45 days by paired t-test of significance and it was found that the mean serum Zn level was statistically significant (P<0.001*) after 45 days of treatment. So it was concluded that the serum Zinc level after Zinconia Tab (20 mg) administration once a day at 15 day, 30 days and 45 days are statistically significant(P<<0.001*) to serum Zinc level at base line i.e. as the time of treatment with Zinconia tab increases, the serum level of Zinc increases (Table.4).

The unpaired t-test is applied to compare mean serum Zinc level in male and female subjects of study population at baseline (0 Days,15 days,30 days,45 days. It was found that the mean serum Zinc level in male and female subjects of study population was statistically non-significant (P<.05) at baseline 0 Days,15 days,30 days,45 days.

Table 4 Showing the comparison of serum Zn level at 0,15,30 and 45th day in study population

		N	Mean (mmol/l)	Std. Deviation	p-value
Pair 1	Zn level 0 day	30	0.00474	0.00144	0.001*
	Zn level 15 day	30	0.00570	0.00104	
Pair 2	Zn level 0 day	30	0.00474	0.00144	<0.001*
	Zn level 30 day	30	0.00664	0.00120	
Pair 3	Zn level 0 day	30	0.00474	0.00144	<0.001*
	Zn level 45 day	30	0.00763	0.00163	

Applied paired t test for significance. *Significant

Table 5 showing the comparison of serum Zinc level in male and female of study population at 0,15,30 and 45th day

	Gender	N	Mean(mmol/l)	Std. Deviation	p-value
Zn level 0 day	Male	16	0.00494	0.00167	0.427
	Female	14	0.00451	0.00114	
Zn level 15 day	Male	16	0.00550	0.00071	0.279
	Female	14	0.00592	0.00131	
Zn level 30 day	Male	16	0.00628	0.00104	0.078
	Female	14	0.00705	0.00127	
Zn level 45 day	Male	16	0.00713	0.00181	0.074
	Female	14	0.00819	0.00121	

Applied unpaired t test for significance.

So it was concluded that serum Zinc level in sex of study subjects does not shows any significant variation.(Table.5). Applied one way ANOVA for significance to compare mean serum Zinc level in all age groups. It was found that serum Zinc level at baseline(0 day),15 day,30 day,45 days was statistically non significant(p<.05) i.e after administration of 20 mg Zinconia tab OD in all age group the serum zinc level has no significant difference.(Table.6).

Table 6 Showing the comparison of zinc level in age groups

		N	Mean (m mol/l)	Std. Deviation	p-value
Zn level 0 day	20 to 40 years	20	0.00492	0.00156	0.597
	41 to 60 years	9	0.00440	0.00121	
	Above 60 years	1	0.00402	.	
Zn level 15 day	20 to 40 years	20	0.00580	0.00099	0.765
	41 to 60 years	9	0.00550	0.00123	
	Above 60 years	1	0.00540	.	
Zn level 30 day	20 to 40 years	20	0.00656	0.00115	0.866
	41 to 60 years	9	0.00682	0.00142	
	Above 60 years	1	0.00650	.	
Zn level 45 day	20 to 40 years	20	0.00737	0.00164	0.504
	41 to 60 years	9	0.00813	0.00166	
	Above 60 years	1	0.00810	.	

Applied one way ANOVA for significance.

The numeric rating scale (Intensity of symptoms) were compared at baseline serum zinc level 0 day followed by 15 days, 30 days and 45 days. The Numeric Rating Scale (NRS-11) is an 11-point scale for patient self-reporting of pain. It is for adults and children 10 years old or older.

Rating	Pain Level
0	No Pain
1-3	Mild Pain (nagging, annoying, interfering little with ADLs)
4-6	Moderate Pain (interferes significantly with ADLs)
7-10	Severe Pain (disabling; unable to perform ADLs)

It was found that at baseline (0 day) most of study subjects have associated mild pain. There was statistically non significant (P>.05) correlation between the mean serum Zinc level and associated mild pain. On 15th, 30th and 45th days of Zinc tablet administration, most of study subjects reported with mild pain however the number of study subjects in mild pain category on NRS scale increases as the duration of Zn intake increases. So It was concluded that as the Duration of Zinc intake increases, the mean serum Zinc level increases and symptoms of pain (NRS) decreases or vice versa. However this co-relation was statistically not significant (P>.05).(Table.7).

The change in symtoms scale (CSS) compared with serum Zinc level at baseline (0) day,15days and 30 days and Applied one way ANOVA for significance. It was concluded that on baseline (0 days), all study subjects (30) have reported significant worsening of symptoms. However on 15th day post administration of 20 mg Zinconia tab, there was slight improvement in symptoms in 24 study subjects. On 30th day, 12 study subjects have significant worsening of symptoms while 14 study subjects have slight improvement. The mean serum zinc level at baseline 0 day, 15th day and 30th was statistically not significantly associated (P>.05) with duration of administration of Zinc tablets. However at 45th day of post Zinc tablet administration, most of study subjects (25) show slight improvement. It was concluded that mean serum Zinc level at 45th day was statistically significant(p<.05) and associated with change in symptoms scale(CSS) i.e the serum zinc level affects the change in symptoms scale (CSS). (Table.8)

The degree of erythema and ulceration in oral lichen planus has been described by Modified oral mucositis index. The degree of erythema is accessed on the scale from 0 to 3. At the baseline (0 days), 11 study subjects have normal oral mucosa followed by 12 study subjects having moderate erythema while in 6 study subjects there was mild erythema. In only one study subject severe erythema has been recorded at baseline. However on 15th day post administration of 20 mg Zinconia tab once a day,12 study subjects have reported with mild erythema followed by 11 study subjects with normal oral mucosa. The 7 study subjects have moderate erythema. After 30th day of Zinc tab administration, the 11 study subjects have no erythema followed by 9 study subjects with mild erythema and moderate erythema of each has been reported..only 1 study subject with severe erythema has been reported with 30th day of zinc administration. After 45th day of Zinc tablet (20mg) administration, 17 study subjects have reported with normal oral mucosa followed by 10 subjects with mild erythema and 3 subjects with moderate moderate erythema. It was concluded that as the mean serum Zinc level increases from baseline to 45th day of zinc administration, there is improvement in erythematous component of modified oral mucositis index but the mean serum Zinc level is statistically not significant(p>.05) with erythematous component of modified oral mucositis index i.e the mean serum Zinc level does not affect the degree of erythema in oral lichen planus patients (Table.9a).

The degree of ulceration in oral lichen planus is accessed on the scale from 0 to 3 in Modified oral mucositis index. At baseline(0) days, the maximum study subjects (12) have ulceration of oral mucosa of .25 to 1cm followed by 0.0 - .25mm in 11 study subjects. However 7 study subjects have ulcer size 1cm/>1cm.

Table 7 Showing the variation in Numerical rating scale (NRS) scale at 0,15,30,45 days in study population

NRS code	At 0 day			At 15 day			At 30 day			At 45 day		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Code 0	2	0.00538	0.00187	2	0.00625	0.00092	2	0.00655	0.00092	2	0.00740	0.00099
Code 1	6	0.00398	0.00073	13	0.00566	0.00115	9	0.00607	0.00159	21	0.00763	0.00173
Code 2	2	0.00572	0.00078	6	0.00526	0.00095	1	0.00670	.	1	0.00650	.
Code 3	9	0.00489	0.00217	4	0.00558	0.00043	7	0.00670	0.00093	4	0.00736	0.00177
Code 4	2	0.00404	0.00002	0	0.00000	0.00000	7	0.00724	0.00101	1	0.00810	.
Code 5	4	0.00448	0.00029	2	0.00626	0.00233	2	0.00601	0.00069	1	0.00980	.
Code 6	0	0.00000	0.00000	3	0.00613	0.00075	1	0.00690	.	0	0.00000	0.00000
Code 7	2	0.00564	0.00225	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000
Code 8	3	0.00491	0.00078	0	0.00000	0.00000	1	0.00820	.	0	0.00000	0.00000
Code 9	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000
p-value	0.764			0.763			0.564			0.809		

Applied one way ANOVA for significance

Table 8 Showing the variation in change in symptoms scale (CSS) at 0,15,30,45 days in study population

CSS code	At 0 day			At 15 day			At 30 day			At 45 day		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Code 0	30	0.00474	0.00144	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000
Code 1	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000
Code 2	0	0.00000	0.00000	0	0.00000	0.00000	2	0.00621	0.00098	0	0.00000	0.00000
Code 3	0	0.00000	0.00000	3	0.00697	0.00090	12	0.00692	0.00086	1	0.00950	.
Code 4	0	0.00000	0.00000	2	0.00555	0.00008	2	0.00646	0.00190	2	0.00464	0.00073
Code 5	0	0.00000	0.00000	24	0.00552	0.00102	14	0.00649	0.00145	25	0.00771	0.00148
Code 6	0	0.00000	0.00000	1	0.00636	.	0	0.00000	0.00000	1	0.00910	.
Code 7	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000	1	0.00810	.
Code 8	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000
Code 9	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000	0	0.00000	0.00000
p-value	NA			0.128			0.778			0.046*		

Applied one way ANOVA for significance. *Significant

However on 15th day post administration of 20 mg Zinconia tab once a day, the maximum study subjects (13) have code 1 ulceration followed by code 2(10 subjects) and code 3(6 subjects) respectively while only 1 study subject have no ulceration. After 30th Day of Zinc tab administration, the 15 study subjects have code 1 ulceration followed by code 2(9 subjects), code 3(5 subjects) and code 0 (1 subject). On 45th day, 22 study subjects have code 1 ulceration followed by code 2(4 subjects), code 3 (2 subjects) and code 0 in 1 study subject. By applying One Way ANOVA test of significance, it was concluded that as the mean serum Zinc level increases from base line(0 day) to 45th day of treatment, the ulceration in study subjects reduces in size and intensity but this co-relation was statistically non significant(P>.05) (Table.9B)

DISCUSSION

zinc enhances the enzyme activity, contributes to protein structure, and regulates gene expression[13]. It is cofactor for polymerases and proteases involved in many cellular functions such as wound repair and intestinal epithelial cell regeneration[14,15].

It is believed that zinc interact with taurine and vitamin A and has antioxidant effects which may protect macular degeneration caused by oxidative stress[16]. The same effect may be considered in the process of the cellular degeneration cause by LP.

Table 9 A Showing the variation in modified oral mucositis impact (MOMI) at 0,15,30,45 days in study population

MOMI code	At 0 day			At 15 day			At 30 day			At 45 day		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Code 0	11	0.00446	0.00106	11	0.00583	0.00127	11	0.00686	0.00149	17	0.00753	0.0018
Code 1	6	0.00604	0.00247	12	0.00546	0.00106	9	0.00629	0.00117	10	0.00782	0.00128
Code 2	12	0.00426	0.00060	7	0.00589	0.00054	9	0.00686	0.00077	3	0.00757	0.00225
Code 3	1	0.00570	.	0	0.00000	0.00000	1	0.00530	.	0	0.00000	0.00000
p-value	0.060			0.609			0.462			0.909		

Applied one way ANOVA for significance

Table 9B Showing variation in modified oral mucositis impact (MOMI) at 0,15,30,45 days in study population (ulcer componebts)

MOMI (Ulcer size) code	At 0 day			At 15 day			At 30 day			At 45 day		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Code 0-(No ulceration)	0	0.00000	0.00000	1	0.00414	.	1	0.00400	.	2	0.00681	0.00381
Code 1(0-.25mm)	11	0.00534	0.00204	13	0.00591	0.00113	15	0.00651	0.00109	22	0.00764	0.00151
Code 2(.25-1cm)	12	0.00422	0.00037	10	0.00546	0.00040	9	0.00683	0.00105	4	0.00825	0.00102
Code 3(1cm, >1cm)	7	0.00466	0.00128	6	0.00588	0.00148	5	0.00720	0.00133	2	0.00710	0.00283
p-value	0.178			0.336			0.088			0.748		

Applied one way ANOVA for significance

Zinc deficiency is associated with impaired wound healing and the other effect is inhibition and stimulation on lymphocyte reaction. Thymic epithelial cells secret thymic hormones that have an impact on the maturation of Tlymphocytes. One of these peptides, thymulin, requires zinc as a cofactor and in an equal molarity ratio for biological activity[15]. The same influence on T-lymphocytes may perhaps be concerned in the process of immunologic-based diseases like LP. Haase *et al*[17] stated that in zinc deficiency conditions, the function, development and the polarization of T-lymphocytes into effectors are disrupted. This process leads to reduction in T-cell numbers, decreased ratio of type 1 /type 2 T-helper cells (with reduced production of T-helper type 1 cytokines like interferon-gamma) and compromised T-cell mediated immune defense. There were limited studies available reporting the zinc level in OLP so this study might be a milestone in research field regarding lichen planus.

In present study, on comparing the numeric rating scale (Intensity of symptoms) with the baseline serum zinc level 0 day followed by 15 days, 30 days and 45 days, it was concluded that as the duration of Zinc intake increased, the mean serum Zinc level increased and symptoms of pain (NRS) decreased or vice versa.However this co-relation was statistically not significant (P>.05). On comparing the change in symtoms scale(CSS) with serum Zinc level at baseline(0) day,15days and 30 days, it was concluded that mean serum Zinc level at 45th day was statistically significant(p<.05) and associated with change in symptoms scale(CSS) i.e the serum zinc level affects the change in symptoms scale(CSS).

Present study concluded that as the mean serum Zinc level increased from baseline to 45th day of zinc administration, there was improvement in erythematous component of modified oral mucositis index but the mean serum Zinc level was statistically not significant(p>.05) with erythematous component of modified oral mucositis index i.e the mean serum Zinc level did not affect the degree of erythema in oral lichen planus patients.it was also observed that as the mean serum Zinc level increased from base line(0 day) to 45th day of treatment, the ulceration in study subjects reduced in size and intensity but this co-relation was statistically non significant(P>.05). Khandpur *et al*[18] did a double-blind randomized controlled study on subacute and chronic eczema, lichen planus and limited psoriasis, 2.5% topical zinc sulfate in combination with 0.05% clobetasol propionate cream (Zincoderm Cream, Apex Laboratories) was found superior to topical steroid use alone, due to the anti-inflammatory properties of zinc sulfate by preventing the release of keratinocyte, an associated marker of inflammation.

Agren *et al*.[19] in his study, topical zinc was used in wound treatment and they concluded that post-operative serum-zinc levels increased (p< 0.001) in both experimental and placebo groups but did show any significant difference between the two groups on day seven. There was no study regarding systemic zinc supplements to LP patients. Above mentioned studies were using topical zinc in treatment of LP.So, the data and outcomes from the present study might be beneficial to future prospects regarding treatment of Lichen Planus.

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