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Serum LDH level: Diagnostic and Prognostic Implications in Oral Squamous Cell Carcinoma

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Abstract:
Background:- *Oral squamous cell carcinoma (OSCC) is the sixth most common human cancer that encompasses at least 90% of all oral malignancies. Serum LDH may be used as a tumor marker for diagnostic and prognostic implication in OSCC.*
Settings and Design*:- Tertiary care hospital, Interventional study*
Conclusion:- *The serum LDH level was significantly (p=0.001) higher among the cases compared to controls at pre-op. There was significant rise in serum LDH level at pre-op which decreased at post-op. The mean change (37.77±358.90) in the serum LDH from pre-op to post-op was statistically insignificant.*

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I. Introduction

Oral cancer presents challenging and unresolved problems for the human population, and for a high-risk region like India it is of prime concern. It constitutes about 3-4% of all cancers in western industrialized countries, mainly affects middle aged and elderly people; and is more common in men compared to women.[1]

In India, where the habits of chewing tobacco with betel nut, reverse smoking and heavy alcohol usage are common, there is a striking incidence of oral cancer, which accounts for as many as 30-40% of all cancers. About 90% of oral cancers are squamous cell carcinomas (OSCCs).[2]

Oral squamous cell carcinoma (OSCC) is the sixth most common human cancer that encompasses at least 90% of all oral malignancies. OSCC is recognized to have 50%, five year survival rate. Considering the ever increasing incidence of OSCC in India and worldwide, there is always a need to find out and standardize easier methods for screening, diagnostic as well as therapeutic purposes. In this view, the biochemical studies could prove to be promising in the future. Biochemical studies in the evaluation of cancer have shown that various substances alter quantitatively in the serum during tumor development.[4]

Tumor markers have been introduced for the early detection of the lesion. These markers have a wide range of potential applications: For screening purpose, diagnosis, prognosis and monitoring the response to treatment. The search for "Ideal tumor marker" has become a major goal in oral pathology.[6]

Identification of such an ideal tumor marker can offer an exciting opportunity for early detection of the lesion. In the oral cavity, various tumor markers have been studied: These include oncofetal protein (α-fetoprotein: Carcinoembryonic antigen), β−2 micro globulin and enzymes (lactate dehydrogenase [LDH]). One such marker is serum LDH.[1] The enzyme lactate dehydrogenase (LDH) is found in the cells of almost all body tissues. It is especially concentrated in the heart, liver, red blood cells, kidneys, muscles, brain, and lungs. Increased serum LDH activity is considered as a marker of cellular necrosis and serum LDH levels have been used as a biochemical marker in diagnosis in various cancers like oral, laryngeal and breast cancer. LDH activity is mainly due to genomic changes during malignant transformation. Increased LDH levels are due to increased mitotic index and more lactic acid production by tumor cells due to breakdown of glycoprotein. As the magnitude of dysplastic changes increase in OSCC it is logical to expect increase in values of LDH.[7]

II. Materials And Methodology

SOURCES OF DATA : Patients were categorized into two groups :

1) **STUDY GROUP**: 60 patients histopathologically confirmed as oral squamous cell carcinoma were selected from the outpatient clinic of department of Oral Medicine and Radiology of Dr. B R Ambedkar Institute of Dental Sciences and Hospital, Mahavir Cancer Sansthan and All India Institute of Medical Sciences, Patna, Bihar from May 2014 to May 2015 in the study group.

2) **CONTROL GROUP**: 10 healthy volunteers with age and sex matched with the study group visiting the outpatient clinic of department of Oral Medicine and Radiology, Dr. B R Ambedkar Institute of Dental

Sciences and Hospital, and All India Institute of Medical Sciences, Patna, Bihar for routine dental checkup were included in the control group.

METHODOLOGY :

CLINICAL INCLUSION CRITERIA:

CONTROL GROUP :

- Age ,sex and risk factors will be same
- Subjects within the age range of 20-60 yrs ,both male and females
- With habit of chewing tobacco in any form
- Group I - 10 Subjects without any lesions

STUDY GROUP :

- Subjects within the age range of 20-60 yrs, both male and females
- With habit of chewing tabacco in any form
- Group II - 60 histopathologically confirmed cases of OSCC.

CLINICAL EXCLUSION CRITERIA:

CONTROL GROUP :

- Systemic diseases known to increase serum LDH levels such as MI, liver diseases ,renal disease, and muscle dystrophy
- Other oral conditions known to increase serum LDH levels like periodontitis and patients having received dental treatment 48 hours prior to the study .

STUDY GROUP :

- Patients treated for cancers (chemotherapy, radiotherapy)
- Systemic diseases known to increase serum LDH levels such as MI, liver diseases ,renal disease, and muscle dystrophy
- Other oral conditions known to increase serum LDH levels like periodontitis and patients having received dental treatment 48 hours prior to the study .

STUDY METHOD

CLINICAL EXAMINATION :

Material used in clinical examination

1. Conventional dental chair with illumination

2. A pair of sterile gloves, disposable mouth mask

3. 2 plain mouth mirrors (No.5), straight probe, tweezers

4. Gauze piece and cotton

5. Glass tumbler with water

A brief case history was recorded and if clinical findings matched with inclusion criteria, the patient was informed about all the procedures to be performed during the study. Following that, if patient was ready to be a part of study, the patient was asked to sign the consent form.

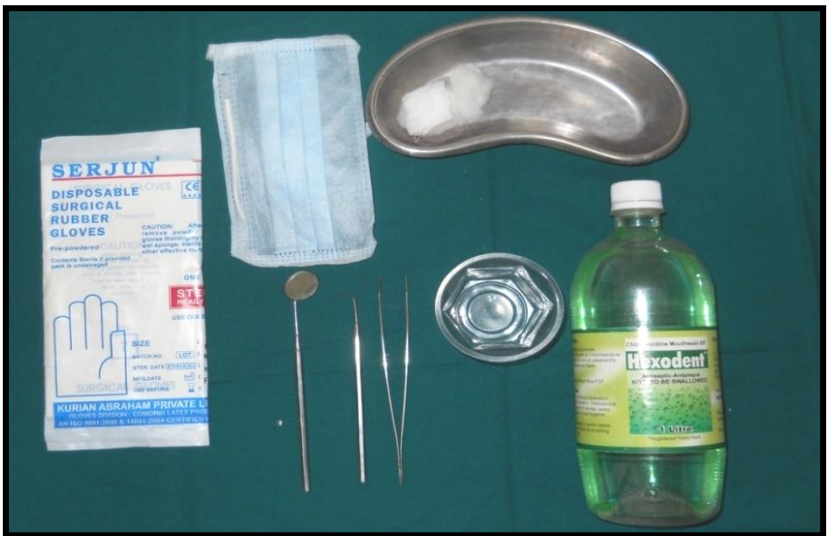

PHOTO 1: ARMAMENTARIUM USED FOR CLINICAL EXAMINATION

HISTOLOGICAL EXAMINATION

Incisional biopsy from the lesion was obtained for all the study subjects and the specimens were preserved in 10% formalin for histopathological diagnosis.

Materials used for biopsy

1. Mouth mirror (No.5)
2. A pair of sterile gloves
3. 2ml sterile disposable syringe with 26 gauge, 1½" disposable needle
4. 2% lignocaine hydrochloride with 1:80,000 adrenaline
5. A sterile biopsy tray
6. BP handle No.3 and No.15 surgical blade
7. Small pointed scissor
8. Surgical hemostat
9. Needle holder
10. Allis tissue holding forceps
11. 3-0 black silk suture
12. Curved suture needle
13. Gauge and cotton
14. 10% Neutral buffered formalin

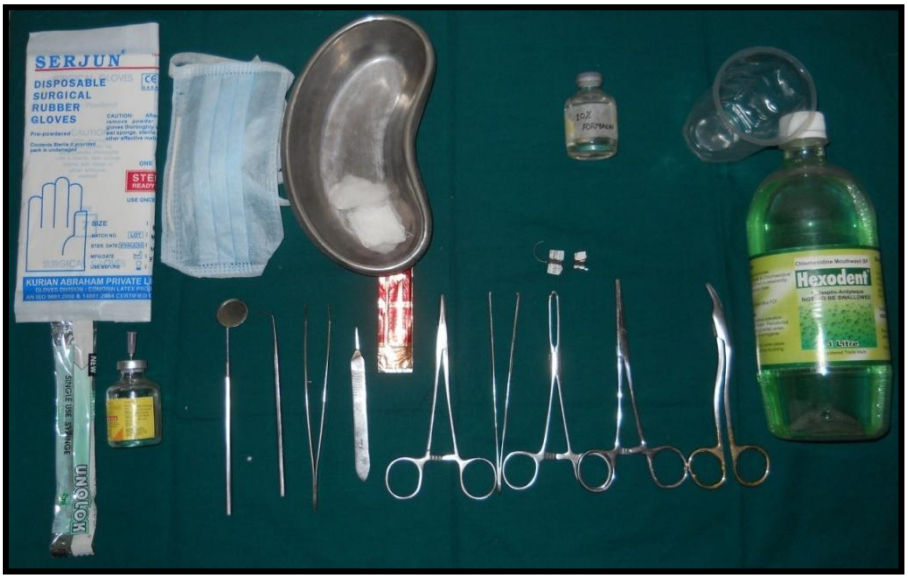

PHOTO 2: ARMAMENTARIUM USED FOR BIOPSY

Procedure for biopsy

Procedure was explained to the patient. Patient was seated on a dental chair and draped with a patient drape. Patient was asked to rinse mouth with water. Local anesthesia was administered. Depending on the site of biopsy, suitable nerve blocks and infiltration were given. Effect of anesthesia was evaluated objectively. After obtaining required anesthesia a semicircular suturing needle was penetrated at site of biopsy and tissue was stabilized using suturing thread. A wedge shape tissue was then incised using B.P. blade. Tissue sample was placed in 10% formalin bottle by taking out stabilizing thread. Site of biopsy was then covered with sterile cotton and pressure was applied to minimize the hemorrhage. Required number of sutures were placed at the site of biopsy which were removed after tissue was healed (Average after 1week). Following biopsy patient was prescribed Amoxycillin 500 mg TID and Ibuprofen 400 mg TID for 5 days.

Histological diagnosis was based on the following histological criteria:

1. Hyperortho- or parakeratosis, usually with acanthosis
2. Necrosis of the basal cell layer often referred to as "liquefaction degeneration"
3. Band of chronic inflammatory cells usually T-lymphocytes in the subjacent connective tissue

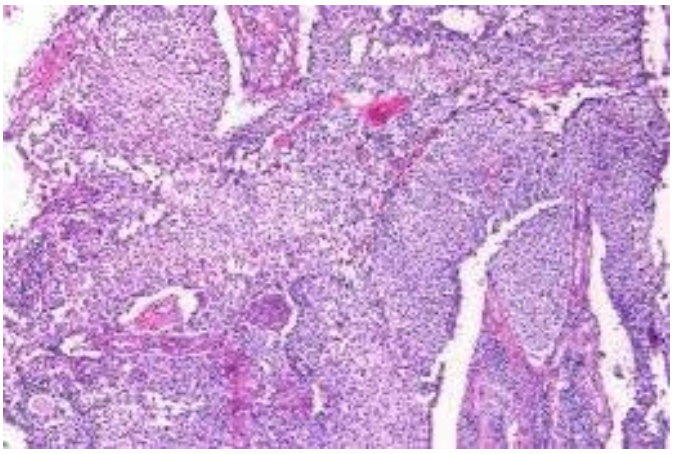

PHOTO 3 : HISTOLOGICAL VIEW OF NON KERATINISING SCC

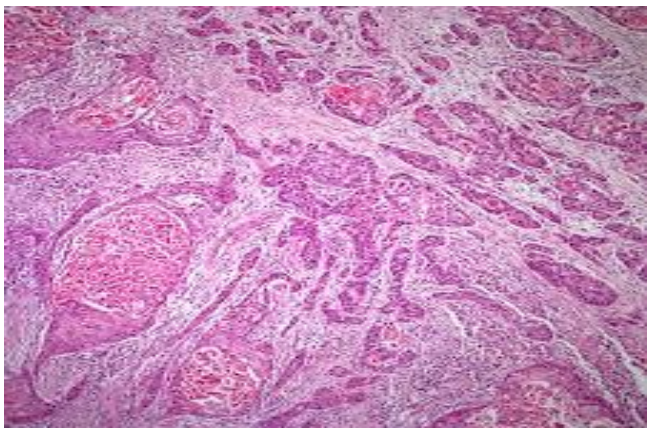

PHOTO 4 : HISTOLOGICAL VIEW OF KERATINISING SCC

BLOOD COLLECTION METHOD

All the aseptic measures were taken and tourniquet was applied 2 inches above the elbow on the upper arm. The site of puncture was cleaned using sterile gauze dipped in surgical spirit. Using 5ml syringe with a 22 gauge 1 ½ inches needle, 4ml of blood was drawn from the antecubital vein. The blood was allowed to clot and the serum separated by centrifugation. The collected serum was stored at -20◦C until use.

STATISTICAL ANALYSIS:-

The results are presented in mean±SD and percentages. The Chi-square test was used to compare the categorical variables. The Unpaired t-test was used to compare continuous variables between the groups. The Paired t-test was used to compare the change in the serum LDH from pre-op to post-op among the cases. The one way analysis of variance was used to compare the biochemical parameters among the clinical stages in cases and histopathological grades. The Pearson correlation coefficient was calculated to find the direction of

correlation between biochemical parameters and age as well as among the biochemical parameters in the cases. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

III. Results

The present study was conducted in the Department of Oral Medicine and Maxillofacial Radiology, A total of 60 cases and 10 controls were included in the study. More than one third of the cases (46.7%) and controls (40%) were above 50 years. The mean age of the cases and controls was 48.45 (±11.72) and 45.30 (±13.23) years respectively. Majority of the both cases (75%) and controls (70%) were males.There was no significant (p>0.05) difference in the gender between cases and controls showing comparability of the groups in terms of gender.

Table-1: Distribution of histopathological grading among the cases

Grade	No. (n=60)	%
Grade 1 KSCC	36	60.0
Grade 2 KSCC	14	23.3
Grade 1non-KSCC	6	10.0
Grade 2 non KSCC	3	5.0
Grade 3 non-KSCC	1	1.7

Table-1 & Fig. 1 shows the distribution of histopathological grading among the cases. The grade 1 KSCC (60%) was found among more than half of the cases followed by grade 2 KSCC (23.3%), grade 1 non-KSCC (10%), grade2 non-KSCC (5%) and grade 3 non-KSCC (1.7%).

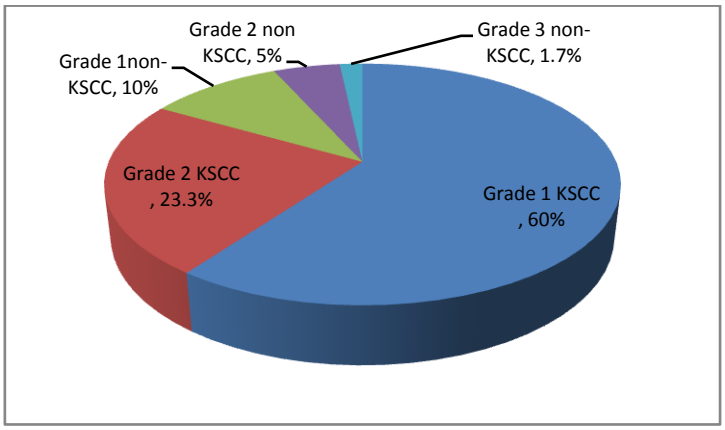

Fig. 1: Distribution of histopathological grading among the cases

Table-2: Comparison of Pre-op serum LDH between cases and controls

Groups	Serum LDH (Mean±SD)
Cases	519.44±196.24
Controls	147.40±24.21
p-value[1]	0.0001*

[1]Unpaired t-test, *Significant

Table-2 & Fig. 2 shows the comparison of pre-op serum LDH level between cases and controls. The serum LDH level was significantly (p=0.001) higher among the cases (519.44±196.24) compared to controls (147.40±24.21) at pre-op.

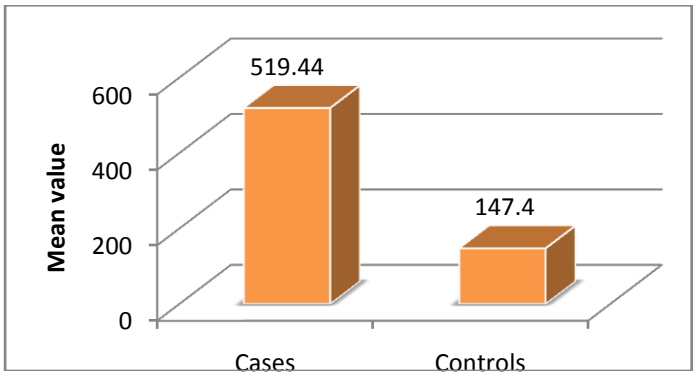

Fig. 2: Comparison of Pre-op serum LDH between cases and controls

Table-3: Comparison of change in serum LDH level from pre-op to post-op among the cases

Time period	Serum LDH (Mean±SD) (n=30)
Pre-op	568.48±221.40
Post-op	530.71±255.81
Mean change	37.77±358.90
p-value[1]	0.56

Table-3 & Fig. 3 shows the comparison of serum LDH level from pre-op to post-op among the cases. The serum LDH level was 568.48±221.40 at pre-op which decreased to 530.71±255.81 at post-op. The mean change (37.77±358.90) in the serum LDH from pre-op to post-op was statistically insignificant (p>0.05).

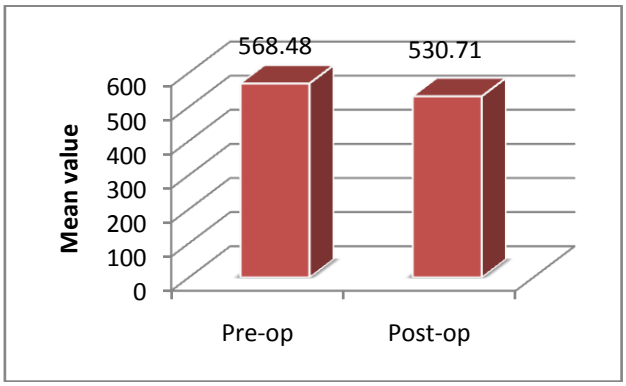

Fig. 3: Comparison of change in serum LDH level from pre-op to post-op among the cases

IV. Discussion

In the present study, a total of 70 subjects including 60 cases and 10 controls were assessed for serum LDH level, and a detailed clinical examination and relevant history of each patient came to the outpatient clinic of Mahavir Cancer Sansthan and All India Institute of Medical Sciences, Patna, Bihar in the study group were recorded thoroughly. The present study was thus carried out to evaluate the serum levels of LDH in patients with OSCC subjects independently and patients came to the OPD for routine checkup, and to probe the possible interrelationships among them so as to utilize this biochemical measurement as an adjunct or alone to diagnose malignant conditions well, before they are clinically or histologically apparent and to monitor the progress of the disease at every step and the prognosis of the disease.

AGE AND GENDER DISTRIBUTION

In present study the age distribution between cases and controls. More than one third of the cases (46.7%) and controls (40%) were above 50 years. The mean age of the cases and controls was 48.45 (±11.72) and 45.30 (±13.23) years respectively.

The gender distribution between cases and controls. Majority of the both cases (75%) and controls (70%) were males.

S. Warnakulasuriya, Oral SCC more frequently affects men than women (M:F = 1.5:1) most probably because more men than women indulge in high-risk habits. The probability of developing oral SCC increases with the

period of exposure to risk factors, and increasing age adds the further dimension of age-related mutagenic and epigenetic changes. In the USA the median age of diagnosis of oral SCC is 62 years. However, the incidence of oral SCC in persons under the age of 45 is increasing.

DISTRIBUTION OF HISTOPATHOLOGICAL GRADING AMONG CASES

In present study the distribution of histopathological grading among the cases, The grade 1 KSCC (60%) was found among more than half of the cases followed by grade 2 KSCC (23.3%), grade 1 non-KSCC (10%), grade2 non-KSCC (5%) and grade 3 non-KSCC (1.7%).

DISTRIBUTION OF PRE OP SERUM LDH LEVEL IN CASES AND CONTROL

In present study there was positive co relation of pre-op serum LDH level with cases(OSCC) compared to controls ,and the statistical data was also significant, The serum LDH level was significantly (p=0.001) higher among the cases (519.44±196.24) compared to controls (147.40±24.21) at pre-op.

Liaw *et al*. in 1997 have shown higher serum LDH values in patients with metastatic disease.

Visjna and Turshijan in 2008 found elevated serum LDH levels in patients with breast cancer and they have opined that elevated level of LDH might be a prognostic sign of disease progression.

Muralidhar *et al*. in 1988 also reported a definite rise of serum LDH levels from normal in premalignant and malignant cases.

Görögh *et al*. studied LDH isoenzymes in human epithelial cells from squamous cell carcinomas and healthy tissues of the oral cavity.

Hariharan *et al*. studied serum LDH and its isoenzymes in buccal mucosa cancer.

Rotenberg *et al*. determined the value for LDH activity in serum and LDH isoenzymes were determined at diagnosis in 273 patients with nonsmall cell lung cancer.

COMPARISON OF CHANGE IN SERUM LDH LEVEL FROM PRE-OP TO POST-OP AMONG THE CASES

In present study there was positive co relation of pre-op serum LDH and post-op LDH, as pre-op LDH was significantly raised compared to post-op LDH, however, the statistical data suggested was not significant. The serum LDH level was 568.48±221.40 at pre-op which decreased to 530.71±255.81 at post-op. The mean change (37.77±358.90) in the serum LDH from pre-op to post-op was statistically insignificant (p>0.05).

V. Conclusion

Based on the observation of our study to assess the relationship of serum lactate dehydrogenase in squamous cell carcinoma of oral cavity, the following conclusions can be drawn:

1. More than one third of the cases (46.7%) and controls (40%) were above 50 years.
2. Majority of the both cases (75%) and controls (70%) were males.
3. The serum LDH level was significantly (p=0.001) higher among the cases compared to controls at pre-op.
4. There was significant rise in serum LDH level, was 568.48±221.40 at pre-op which decreased to 530.71±255.81 at post-op. The mean change (37.77±358.90) in the serum LDH from pre-op to post-op was statistically insignificant.

Thus, it can be inferred that serum lactate dehydrogenase level was significantly raised in oral squamous cell carcinoma patients, In the present study, a total of 70 subjects were assessed for serum LDH level, and a detailed clinical examination and relevant history of each patient were recorded thoroughly. The mean serum LDH level was correlated with clinical and histopathological findings in control group and cases (OSCC).

The progressively increasing serum LDH levels have a positive correlation with histologic grading of squamous cell carcinoma. Estimation of serum LDH level can thus be used to screen cases of oral malignancy though, neither as a strong arbiter nor as a distinct diagnostic test. Its use is only as an auxiliary investigation, which may act as an adjunct to diagnosis and may provide collaborative evidence only. Thus, the present study forms a nidus for further research to be conducted to affirm the absolute utility of serum LDH level as a mass screening test in patients with oral malignancy. Further elaborate studies are required to prove their usefulness in assessing malignant stage condition. Above all, studies including the follow-up of patients are necessary; in order to understand the true value of serum LDH level as a prognostic parameter in OSCC. Serum LDH estimation can prove, to be a valuable biochemical marker; as it is a simple procedure and may be easily accepted by the patients. Although the duration of study was not sufficient to access the prognostic predictive value of serum LDH in OSCC, but study indicate positive correlation between serum LDH at the end of 18 months and poor prognostic in time duration in nasopharyngeal carcinoma, ALL and different types of carcinoma.

It is safe to assume that studies on OSCC with longer follow-up duration may bring to light the prognostic indicative value of serum LDH in OSCC.

Hence the further studies with larger sample size and longer duration are recommended.

Conflict of interest- None
Funding- None

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