Estimation of serum lactate dehydrogenase in smokeless tobacco consumers

Abinaya Chari, Rajesh P, Prabhu S

ABSTRACT

Statement of Problem: Salivary and serum lactate dehydrogenase (LDH) levels have been correlated with potentially malignant lesions. Salivary LDH levels require special testing and can be expensive. The need for a simple and cost-effective analysis tool is essential to detect the oral malignant lesions to benefit rural populations.

Aim: The aim of this study is to estimate the serum LDH in patients with oral lesions due to the consumption of smokeless tobacco.

Materials and Methods: Thirty-five patients with lesions were selected for this study while twenty patients served as a control. Levels of serum LDH were assessed. Age- and sex-matched controls (n = 10) with no smokeless consumption habit and with the habit but without lesion (n = 10) also had their blood drawn to assess the basal level of LDH. The results were then analyzed through the two-tailed t-test and Chi-square analysis using the SPSS statistics software.

Results: The mean LDH value of patients with habit and lesion is 446.8 U/L; the mean LDH value for patients with habit but without the presence of a lesion is 421.2 U/L, and the mean LDH value for patients without a habit or lesion is 269.4 U/L. The patients having the habit of using smokeless tobacco had higher LDH values compared to the other two groups, and it is found to be statistically significant (p < 0.05).

Conclusion: Serum LDH values increased in patients with the habit of chewing smokeless tobacco.

Key words: Oral lesions, serum lactate dehydrogenase, serum marker

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Detection and appropriate treatment at the level of premalignancy can greatly reduce the changes of

Oral squamous cell carcinoma (OSCC) represents about 3% of malignancies in the western population; however, it accounts for over 30% of all malignancies in the Indian population.[1] India has one of the highest rates of oral cancer in the world due to the habit of tobacco chewing;[2] the habit, which is associated with the rural population, illiterate individuals, and those of lower socioeconomic status,[3] is responsible for half of the cancers in men, and quarter of the cancers in women. The frequency of chewing tobacco varies greatly between states (8%–60% in men, <1%–61% in women).[4] The poor prognosis of OSCC is mostly due to the fact that a significant proportion of patients are not diagnosed or treated until they reach an advanced stage.[5] However, the prognosis for patients with OSCC that is treated early has 5-year survival rates as high as 80%, with improved quality of life and fewer invasive surgeries.[5] Thus, prevention of oral carcinoma is divided into two major categories: The reduction of exposure to tobacco and early screening with detailed oral examination and biochemical analysis.[6]

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Although advanced techniques will become imperative in the future of early diagnosis, such techniques are specialized and are not feasible in the rural areas of the Indian subcontinent. Therefore, alternative techniques, which are monetarily more feasible for a rural population, should be explored. For this reason, the application of a simple blood test using a well-known molecular marker, lactate dehydrogenase (LDH), was employed for this study.

LDH is elevated in the serum due to its accumulation in the body tissues. Malignant cells, such as those associated with cancer, have a distinctive type of metabolism, in which the glycolytic sequence and tricarboxylic acid cycle are poorly integrated; hence, the cells tend to utilize five to ten times as much glucose as do normal cells, converting most of it into lactate.

Many studies have seen a correlation between salivary and serum LDH levels in patients with potentially malignant lesions, but there is uncertainty whether LDH levels rise as the lesions increase in severity. Salivary LDH levels require special testing and can be expensive, but serum LDH levels can be measured using a simple and cost-effective blood analysis. This is especially useful in rural populations, where the dentist may not have access to special staining and must rely primarily on clinical knowledge.

The purpose of this study is to explore a simple method of detecting oral cancer in users of smokeless tobacco. The aim of the study is to determine whether oral cancer can be diagnosed early using a simple blood analysis by estimating the serum LDH in individuals who manifest with oral lesions due to the consumption of smokeless tobacco.

MATERIALS AND METHODS

This is a case–control study assessing levels of serum LDH in patients with potentially malignant oral lesions. The study was approved by the Institutional Human Ethics Committee from Chettinad Hospital and Research Institute (IHEC/02/2014/Desp.no. 356). Participants were selected from the Department of Oral Medicine. Eight-hundred patients were screened for this study, and of them, 35 patients with lesions were selected for this study while 20 patients served as a control. Patients aged between 18 and 65 years who had been using smokeless tobacco for a minimum of 6 months and manifested with oral mucosal lesions were recruited for the study. Nonusers of smokeless tobacco, patients currently undergoing treatment for tobacco-related diseases, patients who had other medical problems that can cause an increase in levels of LDH, and patients unwilling or unable to give informed consent were excluded from the study.

Patients in the study were divided into three groups for data purposes [Table 1]:

- Group I - patients who do not have the habit of chewing smokeless tobacco, and without lesion on intraoral examination
- Group II - patients who have the habit of chewing smokeless tobacco, and without lesion on intraoral examination
- Group III - patients who have the habit of chewing smokeless tobacco, with lesion on intraoral examination.

Before the study, each patient was required to sign or stamp informed consent form [Annexure 1]. The study administrator explained the details of the study to the patients in his/her understandable language; furthermore, all questions and concerns of the patients were clarified at that time. Patients were administered an oral questionnaire about their habits [Annexure 2]. On the initial visit, a detailed patient history was obtained, including medical history. Any patient with a previous history of malignancy or other neurological, cardiovascular, gastrointestinal, genitourinary, or respiratory diseases was excluded from the study. A detailed history of tobacco usage was recorded based on the onset, duration, form of tobacco, frequency of consumption, and any break in the habit, and any additional habit including alcohol usage was recorded. A thorough extra-and intra-oral clinical examination was conducted and recorded [Annexure 3], and lesions were photographed. No biopsy was recorded during the study.

After a provisional diagnosis had been reached, a trained phlebotomist collected 5 mL of venous blood sample on the initial visit. Patients were then educated in their regional language about the ill-effects of smokeless tobacco. Empirical pharmacological therapy was administered to each patient based on his lesion and according to the patient’s needs, including vitamins and mineral supplements where necessary.

Levels of LDH in their serum were assessed at Chettinad Hospital Biochemistry Clinical Laboratory. Levels of gamma-glutamyl transferase and serum creatinine were measured using the same blood sample to rule out any liver or kidney disease, respectively. Age- and sex-matched controls (n = 10) with no smoking habit and with smoking habit but without lesion (n = 10) also had their blood drawn to assess the basal level of LDH. The results were then analyzed through the two-tailed t-test and Chi-square analysis using the IBM spss version 23, IBM USA statistics software.
RESULTS

Patients with the habit of using smokeless tobacco who had a lesion on intraoral examination had LDH levels with a range from 236 to 878 U/L [Table 2]. Patients who use smokeless tobacco, but do not manifest with a lesion, showed LDH levels with a range from 361 to 488 U/L. Patients who did not use smokeless tobacco and who did not present with a lesion on intraoral examination had LDH levels ranging from 213 to 355 U/L [Figure 1]. According to the Chettinad Hospital Biochemistry Laboratory, the normal value for LDH is between 180 and 360.

The mean LDH value of patients with habit and lesion is 446.8 U/L; the mean LDH value for patients with habit but without the presence of a lesion is 421.2 U/L, and the mean LDH value for patients without a habit or lesion is 269.4 U/L [Table 3 and Figure 2]. The patients having the habit of using smokeless tobacco had higher LDH values compared to the other two groups, and it is found to be statistically significant ($p < 0.05$) [Tables 4 and 5].

DISCUSSION

The study was conducted with the aim of finding a predictive

Table 1: Distribution of study subjects according to tobacco usage habits

| Group   | Category of patients                              | n   |
|---------|---------------------------------------------------|-----|
| Group I | Number of patients without lesion + without habit of smokeless tobacco | 10  |
| Group II| Number of patients without lesion + habit of smokeless tobacco          | 10  |
| Group III| Number of patients with lesion + habit of smokeless tobacco     | 35  |

Table 2: Serum lactate dehydrogenase in various groups

| Group I | Group II | Group III |
|---------|----------|-----------|
| Serial number | Serum LDH | Serial number | Serum LDH | Serial number | Serum LDH |
| 36 | 222 | 46 | 488 |
| 37 | 274 | 47 | 445 |
| 38 | 202 | 48 | 412 |
| 39 | 267 | 49 | 361 |
| 40 | 355 | 50 | 389 |
| 41 | 328 | 51 | 382 |
| 42 | 213 | 52 | 442 |
| 43 | 242 | 53 | 402 |
| 44 | 253 | 54 | 443 |
| 45 | 338 | 55 | 448 |
| 1 | 320 | 19 | 378 |
| 2 | 524 | 20 | 535 |
| 3 | 503 | 21 | 433 |
| 4 | 245 | 22 | 396 |
| 5 | 343 | 23 | 407 |
| 6 | 299 | 24 | 486 |
| 7 | 356 | 25 | 670 |
| 8 | 261 | 26 | 531 |
| 9 | 325 | 27 | 564 |
| 10 | 236 | 28 | 534 |
| 11 | 362 | 29 | 459 |
| 12 | 366 | 30 | 650 |
| 13 | 238 | 31 | 402 |
| 14 | 628 | 32 | 878 |
| 15 | 542 | 33 | 460 |
| 16 | 540 | 34 | 434 |
| 17 | 444 | 35 | 447 |
| 18 | 440 |   |   |

LDH=Lactate dehydrogenase

Figure 1: Lactate dehydrogenase levels among the study participants
marker for potential malignancy, which can be applied to the rural Indian population. This population was chosen in view of the reports of Rani et al., 2003; Bhawna, 2013; and Boffetta et al., 2008, who noted that the habit of tobacco chewing is increased in the rural Indian population.2-4 The patients reviewed in this study did not consume alcohol, or consumed in minimum quantities (<1 beverage/week) as a means of controlling for smokeless tobacco. In this study, all white lesions were considered. Most of the patients with lesion were diagnosed with either oral submucous fibrosis or leukoplakia. Patients with undermined white lesions that may be leukoplakia or tobacco pouch keratosis were also considered for the study.

Data from the study support the initial hypothesis that LDH levels significantly increase in patients with potentially malignant lesions and, therefore, can act as a viable predictor, in the absence of other medical diseases and conditions, for potential malignancy. However, the study did not find any case of squamous cell carcinoma and the increase in levels in LDH from premalignancy to carcinoma were not checked. In addition, all ten controls who chewed tobacco without having a lesion had elevated LDH levels. These patients should be followed up to find whether a lesion eventually develops or whether LDH value will continue to be elevated in individuals who chew smokeless tobacco, regardless of developing a lesion. Although the levels of LDH increased in almost all the patients with potentially malignant lesions, the LDH values were significantly lower than the values shown by Joshi et al., whose serum LDH values in leukoplakic lesions ranged from 1833.3 to 4734.5.

Furthermore, many types of lesions were accepted into the study. Data were analyzed based on the presence of a premalignant lesion or condition, and not based on a specific lesion (e.g., oral submucous fibrosis). Further testing needs to be performed to determine whether specific lesions can cause more elevated values. This is subject to further analysis.

This study diagnosed lesions purely based on clinical examination, without usage of a biopsy. As biopsy is an invasive technique that can be painful for the patient, the principle of the current study is to find an alternative to such a procedure. Further work needs to be performed to confirm whether the extent of dysplasia correlates with the level of LDH.

In addition, as the study duration was only for 2 months, and since serial LDH values were not measured, significant changes in LDH values over a course of time were not evaluated. In future studies, selected patients should be followed up for 1 year. Further work needs to be performed to determine whether cessation of habit and regression of lesion over a period will correlate with a reduction in the level of LDH.

**CONCLUSION**

Serum LDH values increase in patients with the habit of chewing smokeless tobacco. There is a statistically significant increase in the chances of developing a potentially malignant lesion on the consumption of smokeless tobacco.

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Conflicts of interest
There are no conflicts of interest.

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Annexure

Annexure 1: Patient information sheet

Annexure 2: Subject consent form
Annexure 3: Initial patient questionnaire