SERUM LACTATE DEHYDROGENASE AS A PROGNOSTIC MARKER IN BREAST CANCER

Hardik Tanna[1], Bakane B. C[2]

[1]Post Graduate Student, Department of Surgery, J. N. M. C, Sawangi (Meghe), Wardha.
[2]Professor, Department of Surgery, J. N. M. C, Sawangi (Meghe), Wardha.

ABSTRACT: BACKGROUND: Breast cancer a multifactorial disease and one of the most dreaded of human diseases that claims the lives of thousands of women all over the globe every year. This may probably due to the fact that it remains undiagnosed at an early stage perhaps due to lack of awareness amongst the females and the fact that most cancers do not produce any symptoms until the tumour are too large to be removed surgically. Hence there is need to detect cancer at an early stage.
AIM: Estimation of diagnostic importance and prognostication of serum Lactate dehydrogenase in cases on breast cancer.
SETTINGS AND DESIGN: An observational study was conducted in Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha which included 44 confirmed cases of carcinoma breast and 44 normal healthy females admitted in AVBRH in a span of 2 years.
METHODS AND MATERIAL: Determination of serum LDH was done using TC matrix analyser. The values of LDH were obtained on presentation, 21 days after intervention, 2 months after intervention and 6 months after intervention. The values of LDH on presentation in both the groups were compared. The decline in the values of LDH were observed with the due course of treatment. Chisquare test and Student's Unpaired and paired t test were used for statistical analysis.
RESULT: The mean Lactate dehydrogenase on presentation was in study group and control group was 564.38±219.41 IU/L and 404.18±101.32 IU/L respectively (p<0.05). The levels of Lactate dehydrogenase decreased with due course of treatment. The levels of LDH were proportionate to the stage of disease.
CONCLUSION: The results of the study concludes cost effective usefulness of serum Lactate dehydrogenase in early detection of breast cancer and to assess its prognostic importance which can be done in smaller laboratories.
The traditional model of DS-

INTRODUCTION: Worldwide breast cancer is the most common cancer in females with age-adjusted incidence rates of 124/1,00,000 population in the USA.[1] The incidence of breast cancer is less in India as compared to western countries. The age-adjusted incidence rates ranges from 6.2 to 39.5 per 100,000 Indian women.[2] In India approximately 75,000-80,000 new cases are diagnosed annually as per the cancer registries in the country.[3] A recent report by the Indian Council of Medical Research predicts the number of breast cancer cases in India to rise to 106,124 in 2015 and to 123,634 in 2020.[4]

Research in cancer studies still remains incomplete in spite of the extensive resources being spent on the studies and thus remains an on-going process. Early detection of carcinoma is an important step towards treatment and a number of biochemical markers are being studied to evaluate malignancy and its impact on human survival rate.

Under the normal conditions, each tissue maintains a steady and consistent enzymatic pattern which is significantly altered in malignancy,

because membrane constitutes are shed into the surrounding milieu at increased rate when cells replicated more rapidly.[5] Hence, the enzymes and proteins present in the nucleus, cytoplasm and mitochondria are released into the circulation when cells are destroyed.

These enzymatic changes in malignant tissues may also result from genetic reprogramming to malignant behaviour, a likely strategy for survival of tumour cells. In other words tumour cells can survive extremely well whether oxygen is present or not, thereby allowing for a sort of "one-upmanship" or a competitive advantage over the normal cell when supplies are limited.[6]

Serum Lactate dehydrogenase (LDH) is an enzyme which may rise in malignancies breast cancer and since being economical and relatively easier to estimate, remains as useful and practical marker in terms of prognosis and also early diagnosis.

In view of these observations, the present study was conducted in AVBRH, Sawangi (Meghe), Wardha to study quantitative variations in LDH levels in breast cancer and assess the possibility of using this as prognostic marker.

MATERIALS AND METHODS: In all, 44 females with confirmed diagnosis of carcinoma breast who did not had any previous history of intervention were selected for the present study from Acharya Vinoba Bhave Rural Hospital, Sawangi (Meghe), Wardha.

From these patients detailed information regarding socio-economic status, clinical history, reproductive history and family history of breast cancer and/or other cancers were obtained using specified proforma. Similarly women who fulfilled exclusion criteria (Myocardial infarction, Myocarditis, Liver disorders, Muscular dystrophy, Ovarian cancer, Lung cancer, Haematological diseases) were taken as control. The study group had three subgroups i.e. who underwent surgical management, who received chemotherapy and who did not received any intervention.

Samples were collected from all the patients and the control group on presentation. In the study group serum LDH levels were observed on 21 days, 2 months and 6 months after intervention.

Serum LDH levels were estimated using TC Matrix analysers. Statistical analysis was done using Chisquare test and Student's Unpaired and paired t test. In this study the level of significance was ($P<0.05$).

RESULTS: Serum LDH levels were significantly elevated in patients of breast cancer when compared with the control group. (Table 1)

Group	Mean LDH Values	P value
Study Group	564.38±219.41	4.38,p=0.0001, S, p<0.05
Control Group	404.18±101.32	
Table 1: Comparison of LDH value in Study and Control Group on admission		

Of the study population, premenopausal women had mean LDH 648.57±247.55 while postmenopausal women had mean LDH 525.10±197.21 with a p value of $p>0.05$ which was non-significant.

Stratification of the cohort as per the initial tumour size at presentation yielded the following data, 09.09% (04 patients) with tumour size between 2 to 5 cm (T2 lesion), 54.55% (24 patients) with size >5cm (T3 lesion), 34.09% (15 patients) with T4 lesion and 02.27% (01 patient) with T1 lesion was found in one patient during the study.

Out of 44 patients, 31(70.45%) patients underwent surgical intervention out of which 27(87.10%) patients underwent Modified radical mastectomy while 4(12.90%) underwent Breast conservation surgery. Of the 4 patients of BCS, in 3(75%) patients reconstruction using TRAM flap was done while in the remaining one (25%) patient primary reconstruction was done.

It was also observed that the levels of serum Lactate dehydrogenase increased with the stage of disease. The mean Lactate dehydrogenase in the patients with early stage disease was 482.75±160.48 while patients with late stage disease had mean Lactate dehydrogenase 632.41±241.04 with p value of $p<0.05$ (Table 2)

Stage of Disease	Mean LDH Values	p-value
Early stage	482.75±160.48	2.37 P=0.022, S, p<0.05
Late stage	632.41±241.04	
Table 2: Average Serum LDH values in study population according to the stage of disease		

29(65.91%) patients were followed after 21 days, 25(56.82%) patients after 2 months and 17(38.63%) patient after 6 months. A statistical decrease in the values of serum Lactate dehydrogenase was observed. (Table 3)

	Mean	N	Std. Deviation	Std. Error Mean
0 Day	563.41	29	182.69	33.92
21 Days	435.44	29	128.25	23.81
2 Months	349.08	25	87.00	17.40
6 Months	289.35	17	60.12	14.58
Table 3: Mean Value of Serum Lactate Dehydrogenase at various time intervals				

DISCUSSION: Breast cancer being commonest cancer in Indian women mortality is high due to late presentation. Early diagnosis is of vital importance for prognosis and outcome. Hence there is a need to detect cancer at early stage.

This can be achieved to a certain extent by measuring products and metabolites derived from the tumours in the body. However the analytical method of many of these are unapproachable for general population as the facilities for these are available only at sophisticated and well equipped centres with latest technology and are expensive. Thus, a need is felt for some simple biochemical investigations for the early detection of cancer and can be assayed in smaller laboratories located in remote areas which are cost effective.[7]

Elevated serum LDH levels in patients with carcinoma breast has been estimated by many worker.[8]

Lactate dehydrogenase is an oxidation reduction enzyme which reversibly catalyses the reaction between pyruvic acid and lactic acid. It is distributed widely in body tissues and is raised in variety of physiological and pathological conditions. LDH is thus derived from the tissues and its high levels in serum indicates the destruction of the cells.

Tumour cells exhibit an unusually high rates of glycolysis under both aerobic and anaerobic conditions so as to enable the selection of cells capable of rapid growth under conditions of hypoxia, that are known to prevail in many neoplasm's without adequate blood supply.[6]

The present study was perhaps the first attempt, in a rural tertiary health care centre, to study role of serum LDH in the diagnosis of patients with Carcinoma Breast and to assess its prognostic value.

The incidence of breast cancer in our study is 27.86% which coincides with the ICMR-Population based cancer registry data i.e. 30%.[2]

The mean age at presentation of the disease was 52.3 years with the youngest patient of 35 years and the eldest of 75 yrs.

In accordance with the observations of Nandakumar et al 2004.[9] and Yeole and Kurkure et al 2003,[10] the present study also demonstrated a higher incidence of breast cancer in post-menopausal women with 68.18% of the study population being post-menopausal.

Study by Abdualla Jarari et al (2013).[11] reported that the values of Lactate dehydrogenase in postmenopausal women was higher as compared to that of premenopausal women which is in contrast to our study where the premenopausal women had significantly raised lactate dehydrogenase values i.e. 648.57±247.55 in comparison to that of postmenopausal women 525.10±197.21 with p value of p>0.05. This may be attributed to the aggressive nature of disease in young individuals and advanced disease at the time of presentation.

The maximum number of patients had tumour size more than 5 cm (T3 lesion) i.e. 54.55% (24 patients) with size >5cm (T3 lesion), while 34.09% (15 patients) had T4 lesion which is in contrast to the study by Parmar V et al 2009.[12] in which of 355 patients, 74% had T2 lesion and 9% had T3 lesion. The difference might be attributed to the cases enrolled in their study might be from high socio economic status and educated urban population. Whereas in our study, more than 95% cases are from uneducated, low socio-economic rural population.

In a study of 14 patients, Visnja Bogdanovic et al (2008).[13] Reported that patient of early carcinoma breast had normal values of Serum Lactate dehydrogenase and only in one patient of stage III b the value of Lactate dehydrogenase was raised by 2 folds. The mean LDH was 6.73 ukat/L (402.99 IU/L) in his study which nearby correlates to our present study in which the mean LDH in early stage is 482.75 IU/L.

It was observed that the levels of Lactate dehydrogenase significantly reduced with the due course of treatment. Similar results were reported by Sandhya Mishra et al 2004 [7] and Amritpal Kaur et al (2015).[14] in which the follow up was 21 days and 1 month respectively. The mean value of Lactate dehydrogenase on 21 days in a study by Sandhya Mishara et al 2004.[7] was 360.2 IU/L which was in near correlation to the mean value of Lactate dehydrogenase in our study which was 435.45 IU/L. It was recommended that "1 month seems to be too short period for any significant change to occur in these parameters and a longer follow up is needed to establish prognostic importance of this investigation". Six months follow up is a longest follow up and strength of our study.

Based on our observations in the study we recommend that levels of serum Lactate dehydrogenase should be followed up till 6 months for better prognostic results. Serum Lactate dehydrogenase can be used as a biochemical marker in the diagnosis and determining the prognosis and progress of disease as it correlates with stage of disease. Further large scale studies are warranted in Indian scenario so that serum LDH can be established as marker for breast cancer especially in rural setup.

BIBLIOGRAPHY:

1. Ries LA MD, Krapcho M, Stinchcomb DG, Howlander N, Homer MJ. SEER Cancer Statistics Review, 1975-2005. 2008; November 2007 SEER data submission,

2. National Cancer Registry Program Ten year consolidated report of the Hospital Based Cancer Registries, 1984–1993, an assessment of the burden and care of cancer patients, New Delhi. Indian council of medical research, New Delhi, 2001.

3. Sinha R AD, Mc Donald SS, Greenwald P, Cancer risk and diet in India. J Psotgrad Med. 2003(49):222-8.

4. Programme NCR. Time Trends in Cancer Incidence Rates 1982-2005. Bangalore, India. Indian Council of Medical Research; 2009.

5. Late R K Seth SK, D P Kharb (2003). Serum Biochemical Markers in Carcinoma Breast, ind J Med Sci. 2003;57(8):350-4

6. Maxwell PH DG, Gleadle JM, et, al. Hypoxia inducible ftumour and influenactor 1 modulates gene expression in solid tumour and influences both angiogenesis and tumour growth. Proc Natl Acad Sci, USA. 1197; 94:8104-9.

7. Sandhya Mishra DCSaPS. Studies of biochemical parameters in breast cancer with and without metastasis. Indian Journal of Clinical Biochemistry. 2004; 19(1):71-5.

8. Jagathersan KA JG. Correlation of serum Glycolytic enzymes and acid phosphtase with sites of metastasis in mammary carcinomatosis. BR Med J. 1962; 827:831-4.

9. Nandkumar A GP, Gangadharan P, et al. Development of an Atlas of Cancer in India, First All India Report: 2001-2002. Bangalore. India: National Cancer Registry Programme (ICMR). 2004:12-24.

10. Yeole BB JK, Jussawalla DJ. Trends in breast cancer incidence in greater Bombay: an epidemiological assessment. Bull World Health Organ. 1990; 68:245-9.

11. Abdalla M Jarari SS, Saeid Omer Alsoaeitiv, Nouh M H. Aljarari, Anuradha.A, Jagannadha Rao Peela. Serum levels of LDH and Gamma GT in Libyan Breast Cancer patients. Indian journal of applied research. 2013; 3(12):32-4.

12. Parmar V HR, Nadkarni MS, Badwe RA. Low axillary sampling in clinically node-negative operable breast cancer. Natl Med J India. 2009; 22:234-6.

13. Visnja Bogdanovic ST, Milan Dordevic, Aleksandra Nikolic, Jasminka Mrdanovic, Dimitar Jakimov, Verna Trajkovic, Gorana Bogdanovic, Tatjana Ivkovic-Kapicl, Tihomir Dugandzija, Oncology Institute of Vojvodina, Sremska Kamenica. Activity of lactate dehydrogenase and superoxide dismutase in the circulation of patients with breast carcinoma. Arch Oncol 2008. 2008; 16(3-4):39-41.

14. Amritpal Kaur MM, and Sudhir Khichy, 6(2), 2625-2629. Biomarkers of Carcinoma Breast in Females. International Journal of Recent Scientific Research. 2015; 6(2):2625-9.