

Original Article

Effect of Chemotherapy on Serum Lactate Levels in Malignant Neoplasia

1. Kausar Tasneem 2. Muhammad Ahmad 3. Rahida Karim 4. Mudassir Ahmad Khan
5. Amjad Zaman

1. Assoc. Prof. of Biochemistry, KMC, Peshawar 2. Assoc. Prof. of Biochemistry, PMC, Peshawar
3. Senior Registrar of Peads, KMC, Peshawar 4. Prof. of Biochemistry, KMC, Peshawar
5. Asstt. Prof. of Physiology, KGMC, Peshawar

ABSTRACT

Objective: The present study was designed to look at the levels of serum lactate in various malignancies and to observe the effect of chemotherapy on serum lactate concentration in malignant neoplasia as a whole. The study was also intended to look for the difference, if any, in this effect for haematopoietic and non-haematopoietic neoplasias, so as to see whether evaluation of lactate levels could represent an additional and useful parameter in determining the clinical and prognostic aspect of the disease.

Study Design: Observational and comparative study.

Place of Study: This study was conducted at Radiotherapy Department, Jinnah Postgraduate Medical Centre, Karachi

Materials and Methods: In this study 131 patients of Malignant Neoplasia were taken from the out-door patients in which 56 patients of haematopoietic group and 75 patients of non- haematopoietic group. Blood samples of 131 patients suffering from haematopoietic and non-haematopoietic neoplasia and 20 healthy control subjects were collected and analyzed for lactate, pyruvate and the NADH/NAD⁺ ratio.

Results: Blood lactate, Pyruvate levels and NADH/NAD⁺ ratio were significantly higher in all groups of neoplasia before chemotherapy when compared with control subjects. The NADH/NAD⁺ ratio and the levels of blood lactate and Pyruvate decreased significantly with chemotherapy in all groups of patients suffering from neoplasia.

Conclusion: Observation of low levels of these parameters, particularly that of serum lactate, after the course of chemotherapy can be used as an indicator of prognosis and also considered helpful in assessing the effectiveness of chemotherapy in malignancies.

Key Words: Neoplasia, Haematopoietic neoplasia, Non-Haematopoietic neoplasia, Chemotherapy, Lactate, Pyruvate.

INTRODUCTION

Lactate is produced as a metabolic end product during anaerobic glycolysis by the action of enzyme lactate dehydrogenase on pyruvate. Its concentration is dependent upon concentration of pyruvate in the cytosol, cellular pH and the cytosolic ratio of (Nicotinamide adenine dinucleotide reduced / Nicotinamide adenine dinucleotide oxidized) NADH/NAD⁺ that reflects the redox state of the cytosol.¹

The excessive accumulation of lactic acid in blood is termed as lactic acidosis.² Lactic acidosis in cancer is complex as the regulation of acid production and its utilization is dependent on regulation of several factors.³ Lactic acidosis can be due to a number of different mechanisms including metastasis and dysfunction of liver, which leads to underutilization of lactate, by process of gluconeogenesis in the liver. The body in order to balance the excess negative lactate ions

produced starts retaining positively charged hydrogen ions, and this results in lactic acidosis.⁴

Tumors have been suggested to behave aggressively as vigorous glycolytic systems in which rate of glycolysis is unchecked by oxygen delivery to the tissues.⁵ Several workers have confirmed rapid glycolysis in malignant neoplasia, and if this is unchecked it may result in excessive lactate production.⁶⁻¹⁰ So far the production of lactate has not been compared in different tumours, nor the effect of chemotherapy on lactate levels assessed.

Therefore, the present study was designed to look at the levels of serum lactate in various malignancies and to observe the effect of chemotherapy on serum lactate concentration in malignant neoplasia as a whole. The study was also intended to look for the difference, if any, in this effect for haematopoietic and non-haematopoietic neoplasias, so as to see whether evaluation of lactate levels could represent an additional and useful parameter in determining the clinical and prognostic aspect of the disease.

MATERIAL AND METHODS

The study included before and after first dose of chemotherapy in patients of different types of malignant neoplasia. They were enrolled from amongst the out-door patients of Radiotherapy Department, Jinnah Postgraduate Medical Centre, Karachi. Twenty normal healthy subjects, of comparable age and socio-economic status, with no family history of cancer, from the staff and students were also included in the study as controls. Patients and control group of both sex of 18 years and above were included. Only those patients and control subjects were included who had no history of diabetes, cardiac or pulmonary or hepatic dysfunction. Informed consent was taken from both patients and control subjects.

Patients apart from having malignant neoplasia, and control healthy subjects suffering from any disease such as diabetes mellitus, hypertension, coronary heart disease or any other acute or chronic illness were not included. Patients already undergoing chemotherapy were excluded from the study.

This was a double controlled study in which the normal healthy subjects served as controls for the cancer patients who had not received chemotherapy; they, in turn, served as controls for patients who had received chemotherapy. Fasting blood samples of 131 patients suffering from haematopoietic and non-haematopoietic neoplasia and 20 control subjects were collected and analyzed for lactate, pyruvate and the NADH/NAD⁺ ratio. Lactate and Pyruvate levels were determined by colorimetric method using kit supplied by Sigma Diagnostic, USA, while NADH/NAD⁺ ratio was determined by calculation. Blood was collected for analysis of different parameters before and four (4) weeks after the chemotherapy treatment. The values were expressed as mean \pm SEM, and Student's "t" test was applied for comparison between different groups with p value less than 0.05 (P<0.05) accepted as significant.

RESULTS

The distribution of patients and control subjects, between the ages of 18-60 years, on the basis of sex and diagnosis is given in Table No.1. Male to female ratio in control subjects and patient group was 13:07 and 56:75 respectively. The malignant neoplasia group comprised of 56 Haematopoietic and 75 non-haematopoietic neoplasia patients. The patients and control subjects had a mean \pm S.E.M of 39.46 \pm 1.96 and 37.10 \pm 3.65 years respectively. No statistically significant difference was observed in the mean age of patients and control groups. The distribution of patients in different groups on the basis of diagnosis and chemotherapy can be seen in Table No.2. Out of the

Haematopoietic group 28 whereas of non-haematopoietic neoplasia patients 38 gave an informed consent to further participate in the study. Only one of the patients in non-haematopoietic neoplasia sub-group left the study without any reason and did not return after giving blood sample before chemotherapy.

Table No.3 describes the comparison of fasting blood lactate and pyruvate levels and NADH/NAD⁺ ratio in controls and in patients of malignant neoplasia (as whole group), haematopoietic and Non-haematopoietic neoplasia (as sub-group), before and after chemotherapy. Blood lactate, Pyruvate levels and NADH/NAD⁺ ratio were significantly higher (P<0.001) in malignant neoplasia as whole group having both haematopoietic and non-haematopoietic neoplasia patients, before chemotherapy when compared with control subjects. The NADH/NAD⁺ ratio and the levels of blood lactate and Pyruvate decreased significantly (P<0.001) after chemotherapy in malignant neoplasia as whole group and in all sub-groups of patients suffering from neoplasia when compared with levels of the aforementioned parameters before chemotherapy.

Table No.1: Distribution of Patients and Control Subjects on the Basis of Sex and Diagnosis

Subject	Male	Female
Control (n=20)	13	07
Malignant Neoplasia [Whole Group] (n=131)	56	75
Haematopoietic Group (n=56)	36	20
Non-Haematopoietic Group (n=75)	20	55

Note: Whole Group = Haematopoietic and Non-Haematopoietic neoplasia patients.

Table No.2: Malignant Neoplastic Patients Before and After Chemotherapy

Diagnosis	Before Chemotherapy	After Chemotherapy
Haematopoietic Neoplasia	28	28
1.Non-Hodgkin's lymphoma	07	07
2.Hodgkin's lymphoma	07	07
3.Lymphoid leukemia	07	07
4.Myeloid leukemia	07	07
Non-Haematopoietic Neoplasia	38	37
1.Breast carcinoma	15	15
2. Lung carcinoma	09	08
3. Uterine carcinoma	07	07
4. Thyroid carcinoma	07	07
Total	66	65

Table-3: Fasting Blood Lactate, Pyruvate and Nadh/Nad⁺ Ratio in Controls and in Patients with Malignant, Haematopoietic and non-Haematopoietic Neoplasia Before Chemotherapy (B/C) and after Chemotherapy (A/C).

The values are expressed as mean \pm SEM. Number of cases is given in parenthesis

CONTROL (n=20)	Lactate (mg/dl)		Pyruvate (mg/dl)		NADH/NAD ⁺	
	6.97 \pm 0.59		0.48 \pm 0.02		16.82 \pm 2.27	
	B/C	A/C	B/C	A/C	B/C	A/C
Malignant Neoplasia (Whole Group) (n= 131)	54.98 \pm 4.18* (n+ 66)	10.80 \pm 0.15† (n= 65)	0.88 \pm 0.05* (n= 66)	0.55 \pm 0.01† (n= 65)	70.24 \pm 5.53* (n= 66)	21.81 \pm 1.44† (n= 65)
Haematopoietic Group (n= 56)	67.45 \pm 6.95* (n= 28)	10.53 \pm 0.23† (n= 28)	0.89 \pm 0.08* (n= 28)	0.57 \pm 0.02† (n= 28)	78.80 \pm 9.13* (n= 28)	19.60 \pm 1.13† (n= 28)
Non-Haematopoietic Group (n= 75)	46.84 \pm 4.72* (n= 38)	11.00 \pm 0.20† (n= 37)	0.85 \pm 0.07* (n= 38)	0.54 \pm 0.02† (n= 37)	63.90 \pm 7.40* (n= 38)	23.42 \pm 2.36† (n= 37)

Note:

* P<0.001 as compared to control subjects.

† P<0.001 as compared to patients "before chemotherapy".

Whole Group = Haematopoietic and Non-Haematopoietic neoplasia patients.

DISCUSSION

The microenvironment of a tumour is characterized by oxygen depletion, lactic acidosis and glucose and energy deprivation.¹¹ Lactic acidosis in cancer patients is not common even when the tumor is a rapid growing one. It often develops suddenly, may in few hours become profound and life threatening.¹² Patients, who harbour tumours but are otherwise healthy, may have compartmentalized areas of hypoxemia. These hypoxic neoplastic tissues elaborate lactic acid. This phenomenon has been identified in patients with myeloproliferative disorders such as acute leukemia,^{8,13,14} Hodgkin's lymphomas,¹⁵ lung oat-cell carcinoma,¹⁶ and anaplastic large-cell carcinoma.¹⁷ Within hypoxic tumor regions anaerobic dissimilation of glucose is the sole source of energy generation. The increased need for glucose may aggravate cancer cachexia.¹⁸

Serum lactate levels in patients with haematopoietic neoplasia in our study were found to be significantly higher (P<0.001) as compared to control group. Malignant cells have a distinct type of metabolism in which the glycolytic sequence and the tricarboxylic acid cycle are poorly integrated, hence the cells tend to utilize from five to ten times as much glucose as do normal tissues, converting most of it into lactate¹⁹. Lactic acidosis associated with haematopoietic malignancies such as leukemia,^{8,17} non-Hodgkin's^{20,21} and Hodgkin's lymphomas²¹ in which leukemia cells become hypoxic due to being packed in bone marrow and thus, overproduce lactate.^{22,23}

Lactic acidosis occurring in patients having non-haematopoietic neoplasia associated with extensive

hepatic metastasis has been attributed to impaired lactate utilization.^{1,16,24} However, hyperlactacidemia has also been reported in similar malignancies without hepatic involvement.²⁵ In our study, we found increased levels of lactate in non-haematopoietic neoplasia which correspond with observations of other research workers.^{3,17,26}

Rice and Schwartz²⁶ showed total correction of lactic acidosis after chemotherapy in a patient who presented with widespread small cell carcinoma lungs and rapidly progressive lactic acidosis. Hayek et al²⁷ reported a patient with acute lymphoblastic leukemia presenting with severe lactic acidosis and renal tubular dysfunction, both of which were refractory to conventional management, including peritoneal dialysis, but resolved rapidly with appropriate chemotherapy. Cho and his group²⁸ also reported a case of acute lymphoblastic leukemia with severe lactic acidosis and enlargement of kidney. Hemodialysis and alkalization resulted in no change in blood lactate level. They showed that after starting chemotherapy the lactic acid levels dropped. A group of scientists²⁹ reported a case of non-Hodgkins lymphoma in which leukemic transformation resulted in elevated plasma lactate concentrations. Our study is also in agreement with the above mentioned researchers and showed a significant decrease in the serum lactate levels in haematopoietic and non-haematopoietic neoplasia patients.

Many of the drugs used to treat malignant tumors are directed towards inhibition of DNA replication. These chemotherapeutic drugs are more toxic to cancer cells than normal cells, because cancer cells divide more rapidly. However such drugs also may inhibit normal rapidly dividing cells such as cells of the bone marrow

or cells in the hair follicles³⁰. Pyruvate levels in this study showed almost the same pattern as exhibited by lactate in all groups of patients. The effect of chemotherapy was also similar on these metabolites. This might be due to the fact that effective chemotherapy reduced the number of malignant cells and their activity, leading to decreased glycolysis.

In hypoxia, the phosphorylation in mitochondria is impaired and cellular stores of ATP are depleted. All these homeostatic derangements eventually lead to an increase in NADH/NAD⁺ ratio, hydrogen ion production, and lactic acidosis.^{8,17} Elevated NADH/NAD⁺ ratio is reported in various types of malignant neoplasia,^{3,7,17} which is in agreement with the present study. This NADH/NAD⁺ ratio dropped significantly after chemotherapy in all groups of patients with malignant neoplasia which is in accordance with the work of different research groups.^{1,8,10,13,16,23}

The decline in the concentration of serum lactate, pyruvate and NADH/NAD⁺ ratio after chemotherapy indicates the fact that chemotherapy not only reduces the number of malignant cells but also decreases glycolysis. As a result the processes, that lead to excessive production of lactate and pyruvate and raise the NADH/NAD⁺ ratio, are reversed, due to effective chemotherapy which reduces the number of malignant cells or stops their activity. It can, therefore, be concluded that the levels of these parameters, particularly that of serum lactate, after the course of chemotherapy can be used as an indicator of prognosis and also considered helpful in assessing the effectiveness of chemotherapy in malignancies.

CONCLUSION

Observation of low levels of these parameters, particularly that of serum lactate, after the course of chemotherapy can be used as an indicator of prognosis and also considered helpful in assessing the effectiveness of chemotherapy in malignancies.

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Address for Corresponding Author:

Dr. Muhammad Ahmad
Assoc. Prof. of Biochemistry,
Peshawar Medical College,
Peshawar.
Email: mahmad29@hotmail.com