STUDY OF SERUM PHOSPHOHEXOSE ISOMERASE (PHI) LEVELS IN THE MANAGEMENT OF HEAD AND NECK MALIGNANCIES

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ABSTRACT : *The enzyme phosphohexose isomerase PHI was estimated in 43 patients of head and neck malignancy. The serum level of this enzyme was found to be raised in all the cancer patients. It was found that there were significantly higher levels of serum PHI in cases with metastatic lesions. The rise in PHI values was proportionate with the clinical stage of tumor. 29 Patients, out of 43 who had taken complete treatment were subjected to post therapeutic PHI level estimations and the response to treatment was evaluated. Study showed that estimation of serum PHI levels have significant role in diagnosis of cancer, early detection of residual growth, recurrent growth and secondaries.*

A cancer begins when a cell multiplies in an uncontrolled fashion forming a tumor mass. It is usually assumed to start as a single cell but it will not become clinically detectable until there are 10 tumor cells with a mass of one gram although most tumors are fairly larger than this before being discovered. Moreover the head and neck region consists of a number of cavities with plenty of hidden areas where a cancer may continue to grow till it is too late for curative treatment (Priestman, 1977).

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The need persists for some clinically easy and simple test which can suggest cancer quite early even before the patients become symptomatic, if performed during routine physical checkup.

Early detection of malignancy always have great significance in cancer management.

A large number of biological markers for cancer are the focus of ongoing research in the field of cancer management as they can be used to screen, to aid in differential diagnosis and to aid in therapy by determining tumour burden.

In present study an attempt is made to evaluate the usefulness of estimation of serum levels of phosphohexoisomerase- a diagnostic tool in cases of head and neck cancers. PHI catalysis the reversible conversion of glucose -6- phosphate to fructose-6-phosphate. It was first discovered in skeleton muscles in 1933 by Ohm. PHI activity in most body tissues is high relative to that of the plasma. Liver and muscles containing more than 1000 times the activity of an equal quantity of serum. The erythrocytes contain about 100 times as much as serum.

According to Bodansky (1961) three major factors influence the passage of an enzyme into the serum from tissues

1. Altered production of the enzyme by the tissue.
2. The blocking of the pathway of normal secretion or excretion of the enzyme by an organ.
3. Change in the permeability or integrity of the tissues so that the enzyme leaks out of the damaged cells and passes into the extracellular fluid and then into the serum.

Normal serum levels of intracellular enzymes are produced due to routine destruction of cells. Malignancy may be the cause of accelerated cell death resulting in raised serum PHI levels.

Warburg and Christian (1943) noted that the serum of tumor bearing rats showed increased levels of glycolytic enzymes. Various enzymes have been studied in malignant conditions after this observation viz. alkaline and acid phosphateses, 5'-Nucleotidase transaminases, isocitric-dehydrogenase, phospho-glucomutase, phosphohexose isomerase and alilsterase but most of these studies were made in cases of cancers of breast, liver and prostate and relatively less work has been done on the the study of these enzymes in head and neck cancers.

MATERIALS AND METHODS

The cases were divided into 2 groups :

Control Group - Consisted 20 cases age matched healthy donors of both sexes.

Study group - Included 43 patients of histologically proved patients of head and neck malignancy. Pre and post therapeutic estimation of serum levels of PHI was done in control group and study group by Bodansky (1954) method. Post-therapeutic estimation of LDH was done according to the type of therapy. The patients treated by surgery estimations were done after two weeks of surgery estimations were done after two weeks of surgery while the patients treated by radiotherapy, serum enzyme estimations were made one month after completion of radiotherapy. Repeated serum enzyme estimations were done in regular followup patients.

Control Group - The levels of serum PHI for the control group ranged from 17.5 to 33.8 with mean of 22.40 ± 5.20 unit/ml. The enzyme showed no difference in these activity in relation to age and sex.

OBSERVATIONS

The value of PHI levels for the patients of cancer was significantly higher as compared to control group (Table - I). There was 3 to 4 times increased in the mean serum PHI activity in patients of head and neck cancer in present study. Schwartz et al (1962) reported nearly 2 fold increase while Goel et al, (1986) observed approximately 4 fold increase in serum PHI activity.

The highest mean serum PHI activity has been observed in cancer nasopharynx may be because it is an hidden site and patients report in very advance stage with cervical metastasis. Vaid et al (1974) found serum PHI level raised more significantly in patients of oral cancer : while Rao et al (1976) found it to be least informative in oral cancer. Contrary to present series, Bhatia et al (1979) observed increased serum PHI activity only in 25% of cancer of nose and PNS. Vaid et al (1974) reported significant serum PHI rise in patients with Ca maxilla. This difference can be explained by the fact that in series of Bhatia et al no patient of malignancy nose and PNS had cervical metastasis.

Table - I
Serum PHI Levels (Units/ml) in Different site of Lesion and control

Group	Number of Cases	Serum PHI Level (Units/ml)			
		Range	Mean±SD	t value	p value
Control	10	17.5 - 33.8	22.40 ± 5.20	-	-
Larynx	10	32.0 - 84.8	53.52 ± 18.96	5.0	<0.01
Laryngopharynx	7	44.25 - 84.6	61.58 ± 12.50	7.8	<0.005
Oral Cavity	6	32.0 - 136.0	83.38 ± 38.68	3.8	<0.05
Oropharynx	4	74.25 - 126.0	93.26 ± 22.64	6.19	<0.005
Nasopharynx	2	135.6 - 140.5	138.05 ± 3.46	-	-
Postcricoid	4	36.25 - 84.0	67.06 ± 21.53	4.02	<0.01
Oesophagus	2	40.4 - 78.2	59.3 ± 26.72	-	-
Nose & PNS	6	44.5 - 116.0	75.16 ± 31.58	4.0	<0.05
Miscellaneous	2	82.5 - 88.6	85.55 ± 4.31	-	-

All the values are compared with those of the control.

It seems that probably, the advancement of lesion influences, the serum **PHI** activity more than the mere site of lesion. The mean serum PHI level was higher in the patients with cervical metastasis (Table -II).

Bhatia et al (1979) also had observations similar to the present study. They concluded that alteration in serum PHI level occurred more significantly in cancer cases having cervical metastasis than in those without metastasis. This shows that the lymphatic spread in head and neck cancer definitely affects the enzyme level in serum and its an indicator of metastatic growth.

Results shows that there was no significant difference in level of PHI 1.1 the ulcerative and proliferative growths (Table-Ill). These findings are consistent with the observations of Goel et al (1986). However Bhatia et al (1979) reported higher serum PHI level in patients with ulcerative growth than in proliferative growth.

In present study - the mean serum PHI activity in relation to TNM clinical staging (Table-IV) revealed that the increase was directly proportional to the advancement in the stage of cancer. Goel et al (1986) had similar results. On comparing serum **PHI** levels according to the histological type of cancer it was observed in present study (Table V) that most of patients (86%) studied had squamous cell carcinoma. A significant rise in serum PHI level was found in lymphoepithelioma as compared to other histological types.

Bhatia et al (1979) and Goel et al (1986) did not observed any significant alteration in PHI level in relation to the histology of the tumor.

Initially the study was started with 43 patients but only 29 patients (66%) completed their treatment. The clinical response to the treatment was good in 4 patients. The mean serum PHI activities decrease significantly after treatment in patients who had good response. These values were comparable to the control group (Table-VI), while in patients who had poor response mean serum PHI levels rather increased slightly as compared to their pre-therapeutic levels. These patients of poor response group had very advance serum, even at initial reporting and the disease probably continue to advance either at primary or secondary site, irrespective to the mode of treatment.

As regard to site of lesion approximately 62% patients of cancer larynx had good response while all patients of cancer oropharynx, nasopharynx and postcricoid region had poor response and accordingly the mean serum **PHI** activities altered.

On comparing the mean serum PHI pre and post therapeutic levels, according to the clinical stage it was seen (Table-VII) that levels of these enzymes decreased proportionately in relation to the clinical staging. In stage IV the mean serum **PHI** levels though decreased as compared to their pretherapy level yet were significantly higher than control level.

Table - II
Mean Serum PHI Values with or without Cervical Metastasis

Group	Total No. of Cases	Without Cervical metastasis		With Cervical metastasis	
		No. of cases	PHI	No. of Cases	PHI
Control	10	-	22.40±5.20	-	-
Larynx	10	6	41.13	4	72.9
Laryngopharynx	7	-	-	7	61.5
Oral Cavity	6	4	61.92	2	126.93
Oropharynx	4	-	-	4	93.26
Nasopharynx	2	-	-	2	138.0
Postcricoid	4	3	61.41	1	84.0
Oesophagus	2	2	59.3	-	-
Nose & PNS	6	2	44.55	4	90.47
Miscellaneous	2	-	-	2	85.55
Total/mean	43	17	53.66±10.00	26	93.99±25.81

Table - III
Mean Serum PHI Level in Relation to Character of Lesion

Character of Lesion	No. of Cases	PHI Values	
		Range	Mean ± S. D.
Control Group	10	17.5 - 33.8	22.40±5.20
Proliferative	31	32.0 - 140.5	69.70±30.8
Ulcerative	10	52.6 - 136.0	79.28±28.1

Table - IV
Serum PHI Levels with Clinical Staging

TNM Staging	No. of Cases	PHI Value	
		Range	Mean ± S. D.
Control Group	10	17.5 - 33.8	22.40 ± 5.20
Stage I	2	32.0 - 40.0	36.0 ± 5.60
Stage II	5	32.0 - 56.4	43.4 ± 10.57
Stage III	4	52.6 - 84.8	66.9 ± 13.86
Stage IV	32	36.25 - 140.5	80.24 ± 29.31

In relation to the type of treatment (RT, Surgery or combination of both) and the response obtained it was observed (Table-VIII), that 52% cases of surgery group got good response and another 26% moderate response while in radiotherapy group only 18% cases obtained good response. In combined therapy group only 40% cases had good response. It is evident that since majority of patients of surgery group had favourable response - the mean serum PHI activity decreased significantly in this group as compared to RT group. The patient selected for surgery had limited lesion as compared to patients of RT

Table - V
Serum PHI Value in Relation to Histological Type of Lesion

Histological type of Carcinoma	No. of Cases	PHI Value	
		Range	Mean ± S. D.
Control Group	10	17.50 - 38.80	22.40 ± 5.20
Carcinoma in Situ	2	32.00 - 84.50	58.25 ± 37.12
Sq. Cell Carcinoma	35	32.00 - 140.50	81.78 ± 62.55
Anaplastic Carcinoma	1	98.40	98.40 ± -
Lymphoepithelioma	1	140.50	140.50 -
Adenocarcinoma	2	42.40 - 44.60	43.50 ± 1.55
Nonhodgkins Lymphoma	1	95.00 - -	95.00 ± -

Table - VI
Post Therapeutic Mean Serum PHI Level in Relation to Site and Response of Treatment

	Total No. of Casees	PHI values in Units/ ml of Serum						
		Protherapeutic	No. of Cases	Good Response	No. of Cases	Moderate Response	No. of Cases	Poor Response
Larynx	8	49.65 ± 17.48	5	24.1 ± 0.64	-	-	3	81.8 ± 24.61
Laryngopharynx	4	64.27 ± 13.99	1	24.6 ± -	1	38.8	2	91.0 ± 7.07
Oral Cavity	5	84.34 ± 43.17	2	24.0 ± 1.41	1	35.5	2	116.0 ± 11.31
Oropharynx	4	93.26 ± 22.64	-	-	-	-	4	79.80 ± 13.37
Nasopharynx	1	135.60	-	-	-	-	1	104.00
Postcricoid	1	68.6	-	-	-	-	1	78.00
Oesophagus	1	40.40	-	-	1	32.4	-	-
Nose & PNS	4	72.6	1	24.2	2	34.35± 5.72	1	60.40
Miscellaneous	1	82.50	-	-	1	41.80	-	-
Control Group	10	22.40 ± 5.20						
Total	29	71.26 ± 29.96	9	24.22 ±0.26	6	36.17 ± 3.97	14	87.28 ± 18.31

group who had advance stage lesions contrary to the present study series Goel et al (1986) observed in majority of patients a gradual but significant decrease in serum PHI activity with respect to RT. But in their study there were only 4 cases of stage IV out of 28 as compared to present study where 19 out of 29 cases belong to stage IV. This might probably the cause of not getting significant decrease in PHI levels in present study in RT group.

Goel et al (1986) also observed that decrease in serum PHI activity correlates well with improvement in general condition of patients as assessed clinically suggesting tumor inactivity.

Vaid et al (1974) opined that surgical treatment is superior in restoring serum PHI value to normal similar to present study. They also opined that post therapy value of serum PHI return to normal only when whole of the malignant tissue has been removed completely.

No comparable data were available for serum PHI value in head and neck cancer patients after treatment in relation

Table - VII
Mean Serum PHI Level Pre and Post Therapy in Relation to Clinical Stage

TNM Stage	No. of Cases	PHI Level	
		Pretherapy	Posttherapy
Control Group	10	22.40 ± 5.20	
Stage I	2	36.00 ± 5.60	23.75 ± 13.71
Stage II	5	43.40 ± 10.57	35.02 ± 20.45
Stage III	3	61.00 ± 8.71	57.80 ± 45.76
Stage IV	19	83.90 ± 29.50	66.18 ± 30.94

Table - VIII
Post Therapeutic Mean Serum PHI Level in Relation to Type of Treatment and Response of Treatment. (Control Value of PHI = 22.40 ± 5.20.)

Regime of Treatment	Total No. of Cases	Pretherapeutic of PHI	Good Response		Moderate Response		Poor Response	
			No.	PHI	No.	PHI	No.	PHI
Radiotherapy	17	76.86 ± 31.37	3	23.96 ± 0.56	4	33.75 ± 3.61	10	34.75 ± 18.38
Surgery	7	53.75 ± 22.46	4	24.04 ± 0.71	2	40.10 ± 2.40	1	70.80
Radiotherapy Plus Surgery	5	76.70 ± 29.34	2	24.70 ± 0.70	-	-	3	101.33 ± 13.31
Total	29		9		6		14	

Table - IX
Pre and Post Therapeutic Serum PHI Level in Regular Followup Cases

Case No. With Clinical diagnosis	No. of Cases	Pretherapeutic Level of PHI	Post therapeutic level of PHI	Remarks
No. 4 : Cancer laryngo pharynx with pharynx with secondary neck, stage IV	1	59.5	a) 54.6	Post Radiotherapy and Surgery
			b) 78.6	At Cancer Tonsil (Second Primary)
			c) 86.0	Radiotherapy, stomal recurrence secondaries in neck.
No. 10 : Cancer Laryngopharynx with secondary neck state III	1	70.0	a) 59.9	Post Surgery
			b) 110.0	Stomal recurrence, Sec. neck distant metastasis (Lung bones).
No. 15 : Malignancy trachea and subglotic region stage IV	1	42.4	a) 27.4	Post Surgery.
			b) 25.2	Post Radiation.

to site of lesion, clinical staging and mode of treatment. Repeated estimation of these enzymes in followup period is very informative as seen (Table-IX), in some of cases in the present study. Case No. 4 though showed a good clinical improvement after combined therapy i.e. radiotherapy and surgery, but his serum enzymes level continued to be higher which aroused us with the suspicion of having either recurrence or distant metastasis and then after detail clinical examination there was another primary in tonsil region, by radiotherapy the tonsillar lesion also regressed but, there was continuous rise in serum level of these enzymes and subsequently patient had stomal recurrence and secondaries in neck.

In another interesting case (Case No. 15) after an adequate surgical excision patient had presented but there was significant fall in serum enzymes level and in subsequent followup patient had a very good clinical response. These observations showed that repeated estimation of these enzyme levels in serum during followup period may help in early detection of recurrence even before they are clinically detectable.

Vaid et al (1974) also opined that serum enzymes level came to normal only after complete excision of tumor mass and their level will rise again with recurrence.

Estimation of serum PHI levels is not a confirmatory test for head and neck malignancy. Elevated levels of serum PHI are also found in various other conditions like myopathies, hepatitis, myocardial infarction etc. These alterations in serum PHI levels are also known to occur in the lung, breast and prostate cancers.

CONCLUSION

However the estimation of this enzyme was found to have significant role in diagnosis of cancer, detection of residual growth, response to treatment and early detection of recurrence and secondaries.

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