BLOOD GLUTATHIONE LEVELS IN HEAD AND NECK MALIGNANCIES

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ABSTRACT

Blood glutathione was estimated in fifty patients of head and neck cancer in the age group of 18-76 years and the results were compared with a group of normal healthy controls. Mean blood glutathione level was found to be significantly lowered in patients than the controls. Irrespective of the site, TNM classification, histopathology, and character of lesion, fall in blood glutathione was nearly same in all the patients. The mean level was significantly increased after radiotherapy when compared with the levels before radiotherapy. The decreased levels of GSH in-patients with head and neck cancer, observed in the present study, may be due to its increased utilization by the cells. The results suggest that patients with head and neck cancer have increased oxidative stress.

KEY WORDS

Glutathione, Head and Neck cancer, Radiotherapy.

INTRODUCTION

Amongst the various types of cancers, head and neck cancer is relatively common in India, due to several factors including tobacco chewing and smoking (1). This may be due to free radical species, which play a role in carcinogenesis and produce oxidative cellular damage (2). In carcinogenesis, oxygen active radicals may also damage specific genes that control growth and differentiation of cells during promotion phase. They may also stimulate a more rapid growth and malignancy of cell (progressive phase).

Glutathione (GSH), a tripeptide (L- γ -glutamyl-L-cysteinyl-glycine), is a most abundant intracellular thiol. Chemoprevention by thiols is useful, particularly under GSH depletion, due to toxic agents and cancer associated diseases. GSH is known to be depleted in-patients exposed to carcinogen agents, such as cigarette smoke, air pollutants, occupational exposure, and viral diseases that are typically associated with cancer (3). However, elevated levels of GSH in head and neck tumors and metastatic lymphnodes were

observed by Guichard et al (4). On the other hand, Peters et al (5) showed that mean value of glutathione did not differ significantly between normal, esophageal, and tumor tissues. Due to the conflicting reports, it was planned to estimate blood glutathione levels in-patients with histopathologically proven cancers of the head and neck regions, in the present study. Further, alterations in blood glutathione levels following radiotherapy were also studied.

MATERIALS AND METHODS

Fifty patients of head and neck cancer, in the age group of 18-76 years, were compared with twentyfive healthy controls of the same age group. In all the patients, detailed history was recorded and clinical examination and routine laboratory investigations were done. Patients with acute or chronic Infections, cancers of the other parts of the body or those who had already received treatment for malignancy in any form were excluded. Diagnosis was confirmed by histopathology and staging was done as per TNM classification. Radiotherapy was given to all the cases using telecobalt- 60. Blood glutathione was estimated at the time of admission and after the completion of radiotherapy. 2 ml heparinized blood was drawn and plasma was separated. GSH was estimated according to Beutler et al (6).

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RESULTS

The mean plasma GSH level, in patients with head and neck cancer, was 11.09 ± 0.40 mg/dl. The value was significantly lower ($p < 0.001$) when compared with the control group (21.37 ± 0.37 mg/dl).

According to the primary site of growth, the patients were divided into 6 groups (Table I). When compared with each other, the fall in blood glutathione was nearly to the same extent in all the groups.

Table I : Blood GSH levels in relation to the site of lesion in Patients with head and neck cancer

Group	Blood GSH (mg%)	
	n	Mean $\pm$ SEM
Control	25	21.37 ± 0.37
Oropharynx	15	$10.62 \pm 0.68^*$
Larynx	13	$11.10 \pm 0.64^*$
Hypopharynx	10	$11.81 \pm 0.70^*$
Esophagus	6	$11.74 \pm 1.02^*$
Nasopharynx	3	$7.80 \pm 0.71^*$
Nose	3	$12.93 \pm 2.60^*$

n = number of subjects; * Difference statistically significant when compared with the control group ($p < 0.001$)

Histopathologically, 47 patients had squamous cell carcinoma (94%), two adenocarcinoma (4%), and there was only one case of adenocystic carcinoma (2%). The mean value of GSH in patients with squamous cell cancer was significantly lower as compared with the control ($p < 0.001$; Table II).

Table II : Blood GSH levels in relation to histopathology

Group	Blood GSH (mg%)	
	n	Mean $\pm$ SEM
Control	25	21.37 ± 0.37
Squamous cell carcinoma	47	$10.82 \pm 0.41^*$
Adenocarcinoma	2	12.75
Adenocystic carcinoma	1	14.95

n = number of subjects; *Difference statistically significant when compared with the control group ($p < 0.001$)

According to the character of lesion, 34 patients showed proliferative type of growth while 16 patients showed ulcerative growth. The mean values for GSH in the two groups were

Table III : Blood GSH levels in relation to the character of lesion

Group	Blood GSH (mg%)	
	n	Mean $\pm$ SEM
Control	25	21.37 ± 0.37
Proliferative	34	$11.22 \pm 0.52^*$
Ulcerative	16	$10.87 \pm 0.79^*$

n = number of subjects; *Difference statistically significant when compared with the control group ($p < 0.001$)

significantly lower when compared with the control group ($p < 0.001$; Table III). According to the nodal status, mean values of GSH in-patients were decreased with the increasing stage of the nodal metastasis (Table IV).

Table IV : Blood GSH levels in relation to nodal Metastases

Group	Blood GSH (mg%)	
	n	Mean $\pm$ SEM
Control	25	21.37 ± 0.37
N ₀	11	$13.30 \pm 0.091^*$
N ₁	22	$11.45 \pm 0.33^*$
N ₂	7	$8.11 \pm 0.47^*$
N ₃	4	$7.25 \pm 0.59^*$

n = number of subjects; *Difference statistically significant when compared with the control group ($p < 0.001$)

Postradiotherapy value of mean GSH was significantly higher when compared with the preradiotherapy level ($p < 0.001$) but however, remained lower than the control group ($p < 0.01$; Table V).

Table V : Effect of radiotherapy on blood GSH level

Group	Blood GSH (mg%)	
	n	Mean $\pm$ SEM
Control	25	21.37 ± 0.37
Patients		
Preradiotherapy	50	$11.09 \pm 0.40^*$
Postradiotherapy	48	$18.24 \pm 0.30^{**}, +$

n = number of subjects; *Difference statistically significant when compared with the control group ($p < 0.001$); ** $p < 0.01$; + Difference statistically significant when compared with the preradiotherapy value ($p < 0.001$)

DISCUSSION

Results of the present study demonstrate that mean blood GSH level was significantly reduced in-patients with head and neck cancer as compared to the control subjects. The fall was

nearly 50% and nearly to the same extent in all the patients, irrespective of site of lesion, its histopathology or character of growth. There was a decrease in blood GSH as the stage of cancer increased. The decreased levels of GSH, observed in the present study, may be due to its increased utilization. Studies suggest that the variant genotypes result in diminished activity of glutathione-S-transferase, which in turn may lead to decreased ability to detoxify carcinogenic and mutagenic compounds. It is possible that this polymorphism may confer an increase in cancer susceptibility (7). A reduction in GSH levels has also been reported in carcinoma of the stomach and the colon (8). On the other hand, Peters et al (5) reported that glutathione levels do not differ significantly between the esophageal normal tissue and the tumor tissue. Whereas elevated levels of GSH have been reported in chronic myelogenous leukemia, acute myelogenous leukemia, or chronic lymphocytic leukemia (9-11). Singh et al (12) observed increased levels of γ -glutamyl transpeptidase in-patients with head and neck cancer. This enzyme is known to cause GSH utilization. Reduced GSH contents have also been reported in rats, in chemical carcinogenesis, by Fiales et al (13).

After radiotherapy, blood GSH levels showed an elevation, in-patients, and the mean value became comparable with the control group. This rise may be due to a decrease in the tumor load, as a result of radiotherapy, which may reduce oxidant stress and improve antioxidant system in such patients. Similarly, vitamin E levels were increased after radiotherapy compared to their pre-radiotherapy levels, in-patients with head and neck cancer (14).

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