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HAEMATOLOGICAL AND BIOCHEMICAL CHANGES IN PRE AND POST TREATMENT OF BUCCAL MUCOSA CARCINOMA PATIENTS

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ABSTRACT: Oral squamous cell carcinoma is one of the leading causes of mortality in India. The various haematological and biochemical changes including liver enzymes imbalance occur in cancer treatment. The careful monitoring of serum biochemical and haematological changes had very important role in prognosis of disease. Therefore, the present study aimed to study haematological and biochemical changes in pre and post treatment of buccal mucosa carcinoma patients. In study, totally 198 buccal mucosa carcinoma subjected were included from both genders. We observed the Haematological parameters (level of completer haemogram, differential leucocytes count), biochemical and liver function parameters in pre and post treatment of subjects. The serum biochemical and haematological levels were lower in post treatment groups than before treatment of subjects, whereas glucose level did not show significant changes. Hence, the subjects did not affected by diabetics. Most of subjects had anaemic, treatment severely affected bone marrow. However, these changes were exists statistically significant by paired samples t-test at $p<0.001$. The biochemical and haematological changes were additional risk for subjects. Thus, these changes will help the prognosis and proper monitoring of the cancer subjects.

INTRODUCTION: Oral cavity squamous cell carcinoma is one of the leading causes of cancer related death in developing countries particularly India.[1] A total of 274,300 new cases recorded worldwide in 2002; almost two thirds were in developing countries. The high risk in Indian population was related to the popularity of pan tobacco (combination of betel leaf, lime, areca nut and sun cured tobacco) chewing in the region. [2] Inflammatory cytokines could promote the production of white blood cells (WBC's).

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Bone marrow produces both red blood cells and white blood cells from the same precursor of stem cells. Therefore, the up regulation of WBC's causes fewer stem cells to differentiate into red blood cells. This may be an important cause for the effective inhibition of erythropoiesis, even when erythropoietin levels were normal. [3] Ernest reported that cytokines suppressed erythropoiesis by affecting red cell production and impaired iron utilization in cancer patients. Thus, ion had an important role in cancer treatment.[4]

Cancer therapeutics such as radio and chemotherapies act as alkalising agents and lead to progressive depletion of hematopoietic stem cells in the bone marrow. This may lead to long-term anaemia, which make the treatment less effective. Overall, the presence of anemia in cancer patients increased the relative risk of death by 65%. Anemia

was associated with decreased survival, decreased tumor response, delays in therapy, reduced patient compliance, and directly retracts from patient's therapeutic outcomes.[4]

Any kind of severe disease or abnormality (especially cancer) has a direct impact on blood parameters so it is necessary to study the changes in haematological and biochemical parameters in cancer patients, at regular intervals during treatment. A complete blood count and biochemical parameters were a blood test that gives important information about the kinds and numbers of cells in the blood, especially red blood cells, white blood cells and platelets. Complete blood count helps health professional check any symptoms, such as weakness, fatigue, or bruising, patient may have. It also helps in the diagnosis of other diseases.[5]

The previous study reported that haematological and biochemical parameters had been remaining unchanged if proper care was taken to avoid side effects in cancer treatment.[6] In view of this present study was undertaken to assess whether adverse biochemical and haematologic effects in buccal mucosa carcinoma subjects and to comparatively analyse the haematological and biochemical changes at the time of diagnosis as pre-level and after treatment tobacco as post-level.

MATERIALS AND METHODS:

The retrospective observational study was carried out in Arignar Anna Memorial Cancer Hospital and Research Centre, Kanchipuram. The present study included 198 buccal mucosa carcinoma subjects among both genders.

The institutional ethical committee permission from directorate of medical education (DME), Tamil nadu was obtained to conduct the study (No.24984).

Sample collection:

After overnight, from each subjects 5ml of venous blood samples were obtained from vein puncture from buccal mucosa carcinoma subjects at the time of diagnosis (pre-level) and within 30 days of treatment (post-level) in plain vacutainer tube without any anticoagulant and kept in tilted position for 30 minutes. After clotting at room temperature, the serum was separated from the clot by cooling centrifugation at 3,000 rpm for 10 minutes. The clear supernatant was immediately transferred in another test tube and used for serum haematological and biochemical analysis.

Analysis of haematological parameters:

The haematological parameters were estimated on a Coulter Counter ZF6 with a haemoglobinometer attachment. Haemoglobin (Hb) was determined spectrophotometrically (540 nm) using cyanomethemoglobin method. Red blood cell (RBC) and White blood cells (WBC) counts were made in Neubauer chamber by mixing with dilution fluids. Platelet Count was analyzed by Sysmex Automated Haematology Analyzer XT-2000i /XT-1800i by using flow cytometry. Mean levels were calculated according to previously published procedure.[7]

Biochemical analysis:

All biochemical analyzes were performed in semi-automatic biochemical analyzer (Autoanalyser, Olympus AU400) using commercial kits. The determination of blood urea was performed by using urea kit from DiaSys Diagnostic Systems GmbH, absorbance was read at 578nm. Creatinine level was estimated according to the colorimetric method (alkaline picrate - Jaffe) with 520nm and alkaline phosphatase according to the colorimetric method at a wavelength of 590nm. Total Bilirubin and conjugated in serum was estimated using kit from Ranbaxy Diagnostics Ltd., New Delhi, India at 546nm. Estimation of Glucose in serum was done by using glucose kit from DiaSys Diagnostic Systems GmbH. All biochemical reactions were processed at 37°C according to the instructions of the manufacturers.

Evaluation of Liver Function Tests (LFT):

Serum alkaline phosphatase (ALP), alanine aminotransferase (ALT; formerly serum glutamicpyruvate transaminase-SGPT) and Serum aspartate aminotransferase (AST; formerly serum glutamateoxaloacetic transaminase-SGOT) were measured.[8] Serum total protein and albumin were analyzed using the Biuret and Bromocresol green methods respectively. In both cases, commercially available test kits, products of Randox laboratories,

U.K. were used and with the manufacturer's instructions strictly adhered.

Statistical analysis:

For statistical analysis SPSS 16 was used. The biochemical results were compared between pre and post treatment using the paired *t*-test.

RESULTS:

The general subject's characteristics were detailed in **Tables 1**. From 2013-2015, the buccal mucosa carcinoma unit treated 198 subjects with both definitive radio-chemotherapy or post operative adjuvant radiotherapy and chemotherapy. The haematological and biochemical changes were observed at the time of admission and after treatment in the study group. The median age of all patients was 54 years (range 23-87 years). There were 125 (63.1%) males and 73 (36.9%) females in the (2:1) ratio. At diagnosis, 21% subjects were diagnosed with stage I/II disease whereas 75% had stage III/IV disease. The haematological parameters observed were Hb, Red cell count, platelets count, total leucocytes count, percentage of granular (neutrophils, eosinophils and basophils) and agranular (lymphocytes and monocytes) leukocytes of all groups. The mean and standard deviation of haematological values were lower in post treatment group than pre level. This haematological changes exists statistical significant at $p<0.001$ as reflected in **Table 2**. After treatment subjects had diagnosed with sever anaemic (6.52±1.26) which affects their quality of life (**Table 3**).

TABLE 1: DEMOGRAPHIC AND CLINICAL CHARACTERISTIC OF BUCCAL MUCOSA CARCINOMA PATIENTS

Characteristic	Total patient number	%
No. of patients	198	
Age (years)		
<50	79	39.9
≥50	119	60.1
Gender		
Male	125	63.1
Female	73	36.9
Site of tumor		
Right	69	34.8
Left	129	65.2
stage of tumor		
Early stage (I/II)	30	15.2
Advanced stage (III/IV)	168	84.8
Histopathology		
well differentiated	98	49.5
moderately differentiated	68	34.3
poorly differentiated	32	16.2
Treatment modality		
Radiotherapy only	59	29.8
Radiotherapy and Chemotherapy	79	39.9
Post operative radiotherapy (PORT)	25	12.6
PORT and Chemotherapy	35	17.7

TABLE 2: COMPARISON OF HAEMATOLOGICAL PARAMETERS IN PRE AND POST TREATMENT OF SUBJECTS

Biochemical Study	Reference level	Pre-Treatments	Post-Treatment	t-value	p value
Complete haemogram					
Total white blood cells (WBC)	3.5-10.5 billion cells/L	7.23±2.12	4.72±1.77	34.05	0.000*
Total Red Blood Cells (RBC)	3.8-4.8 milli/cumm	4.1±0.44	2.48±0.59	41.35	0.000*
Haemogloblin(Hb)	12-17.5 g/dL	9.73±0.98	6.52±1.26	17.39	0.000*
Platelets	150000-450000/ microliter mm3	380400±14360	22430±10240	24.78	0.000*
Differential WBC count					
Neutrophils	40 - 80 %	60.17±11.87	41.91±10.37	19.37	0.000*
Lymphocytes	20 - 40 %	31.36±5.56	25.04±5.5	13.19	0.000*
Eosinophils	1 - 4 %	2.71±0.89	2.01±1.36	6.03	0.000*
Basophils	0 - 2 %	1.12±0.67	0.655±0.494	23.88	0.000*
Monocytes	2- 10 %	5.49±2.33	3.588±1.63	25.79	0.000*

*Statistically significant at $p<0.001$

TABLE 3: COMPARISON OF BIOCHEMICAL PARAMETERS IN PRE AND POST LEVELS OF SUBJECTS

Biochemical Study	Reference level	Pre-Treatments	Post-Treatment	t-value	p value
Glucose (mg/dL)	70-110	101.24 ± 22.36	93.97 ± 20.91	22.458	0.000*
Urea (mg/dL)	20-40	26.43 ± 6.77	25.9 ± 6.9	3.527	0.001*
Creatinine (mg/dL)	0.7 - 1.4	0.82 ± 0.11	0.72 ± 0.12	19.143	0.000*
Uric acid (mg/dL)	3.0-7.2	5.08 ± 1.09	4.2 ± 1.03	23.798	0.000*
Total Bilirubin (mg/dL)	0.5-1.0	0.65 ± 0.18	0.51 ± 0.17	13.048	0.001*
Direct Bilirubin (mg/dL)	Upto 0.3	0.24 ± 0.05	0.18 ± 0.04	19.908	0.000*
Total protein (g/dL)	6-8	6.9 ± 0.64	6.2 ± 0.79	18.771	0.000*
Albumin (g/dL)	3.5-5	4.2 ± 0.46	2.8 ± 0.40	28.29	0.000*
SGOT (U/L)	15-40	21.55 ± 4.7	18.35 ± 4.05	15.613	0.000*
SGPT (U/L)	15-35	26.25 ± 7.74	20.9 ± 6.3	23.593	0.000*
Alkaline phosphatase (U/L)	40-125	75.05 ± 14.2	61.4 ± 13.06	27.197	0.000*

* Statistically significant at $p<0.001$

The biochemical and metabolic parameters observed were glucose, urea, uric acid, creatinine and bilirubin levels of both groups and liver enzymes total protein, albumin, globulin, SGOT, SGPT and alkaline phosphatase (ALP) were estimated. Blood glucose level was assayed with the help of one pick glucometer. These results showed that the values were not significant ($p<0.001$) and there was not much change when compared to that pre treatment value, which indicate subjects did not affect diabetes (**Table 3**). Whereas, urea, uric acid, creatinine, bilirubin and conjugated bilirubin were lower after treatment. Hence, the study revealed that there was significant changes observed pre and level of biochemical values at $p<0.001$ (**Table 3**).

Liver metabolising enzymes, aspartate aminotransferase (SGPT), alanine aminotransferase (SGOT) and alkaline phosphatase (ALP) enzymes were normal before treatment but due to radiation and chemotherapy, post level subjects had significant changes. Similarly, total protein, albumin and globulin also decrease than prelevel of subjects. **Table 3** shown the highly significant by one way paired samples test at $p<0.001$.

DISCUSSIONS: Oral cancer is a frequent problem with significant rates of mortality, an enormous impact on quality of life and morbidity. Development of severe haematological and biochemical changes in oral cancer patients results in prolonged hospitalization increased cost, anaesthetic or surgical difficulty and treatment interruption. Using proper investigations that can identify the patients at higher risk for developing post operative infections, bleeding emergencies and delayed healing, would enable surgeons to individualize surgical treatment protocols.[8-9]

Radiotherapy is one of the tools for treatment of cancers and due to the Co^{60} radiation the biochemical and haematological profile was changed because the Kidney and liver functions were affected.[10] From the various studies it had been observed that different biochemical and haematological profile may get slightly altered due to describe change in metabolic rate as well as toxicities induced by different therapy.[6]

In buccal mucosa carcinoma subjects, a change of biochemical levels during the time span 30 days was noted. In the present study, > 82% of the subjects invariably developed anaemia in that most of them had diagnosed with advanced stages where treatment options were limited and mainly as palliative care. The factors responsible for anemia in cancers include, the neoplastic process itself, due to products of the cancer circulating in the blood or may be due to the cancer treatment. It had been reported that anaemia was associated with poorer prognosis and increased mortality.[10] Aspartate aminotransferase (SGPT), alanine aminotransferase (SGOT) and alkaline phosphatase (ALP) enzymes was located in hepatic cell and when these cell damaged and transaminase were released in the blood stream, the value of these enzymes before starting their treatment showing normal value but after treatment values were slightly decrease, as similarly observed in the present study.[6]

Tumor markers were used for the detection of risk, population screening, diagnosis, staging and prognosis. These biochemical variations could also predict the response to therapy, monitor treatment,

detect presence of occult metastatic disease and monitor the course of the disease.[11] Several tumor markers are in vogue now a days, which include alpha-feto protein, Carcino embryonic antigen, Human chorionic gonadotrophin, Prostate specific antigen and relatively less specific makers like Lactate dehydrogenase, Alkaline phosphatase, ferritin and Gamma glutamyl transpeptidase etc.[12]

Earlier studies reported that 21 days (3 weeks) of surgery seems to be too short a period for any significant change to occur in biochemical parameters and a longer follow up was needed to establish prognostic importance.[6] Hence, our study conducted with minimum samples immediate after treatment, further follow-up studies with large samples were warranted.

CONCLUSION: This study was revealed the significance of haematological and biochemical variations in the form of metabolic changes in buccal mucosa carcinoma subjects, which would be eventually helpful in early diagnosis of oral cancer and also these haematological and biochemical finding could be use as clinically valuable prognostic indicators to assist in more selective treatment options for oral cancer subjects.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interests.

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