

“Role of Bioelectric Impedance Phase angle in Tongue Carcinoma – A Hospital Based Study”

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Abstract: One of the greatest management challenges for the head and neck oncologist is neoplasia of Tongue because of the adverse effects of treatment on oral and pharyngeal function. Diagnosis at later stages results in low treatment outcomes with considerable costs to patients. In these malignancies, Bioelectric Impedance Analysis (BIA) derived Phase Angle affords an emerging opportunity to assess prognosis.

Aims and Objective: To compare the Phase Angle between patients of biopsy proven anterior 2/3rd squamous cell carcinoma tongue and their matched control with the help of Bioelectric Impedance Analysis (BIA) to formulate some guidelines, if any.

Material and Methods: This prospective study was conducted on patients of biopsy proven squamous cell carcinoma of anterior 2/3rd tongue in the Department of General Surgery of subharti medical college admitted through surgery OPD and emergency or transferred from other department after taking informed consent and clearance from University Ethical Committee on 74 patients of tongue malignancy with their matched control during July 2012 to October 2017 (64 months). A total of 74 male cases of histological proven anterior 2/3rd squamous cell carcinoma tongue with their matched controls were assessed for Phase Angle measurement by BIA BODY STAT QUAD SCAN 4000.

Statistical analysis: The data was analysed with Graph pad prism software version 6.03 and Microsoft excel. Phase angle of test group was compared with that of control group by applying unpaired ‘t’ test. One way ANOVA was applied to compare the mean phase angle of different stages and results were statistically significant.

Results: In control group Phase angle showed a mean \pm SEM 5.659 (0.0713) while in test group it showed a mean value \pm SEM 3.643 (0.0548). This study demonstrated that decreasing phase angle is a predictor of presence and increasing staging in carcinoma tongue patients.

Keywords: Bio Electrical Impedance Analyzer, Squamous cell carcinoma tongue, Phase Angle, Reactance, Resistance.

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I. Introduction

There is a significant difference in the incidence of oral cancer in different regions of world, with the age adjusted rates varying from over 20 per 100,000 population in India, to 10 per 100,000 in U.S.A and less than 2 per 100,000 in Middle East.^[1] The tongue is the most common site for oral malignancy. Peak incidence is seen in the sixth decade for men and in the seventh decade for women. In India, this increased number of cases is due to tobacco chewing, smoking and alcoholism. Malignancies of tongue represent one of the greatest management challenges for the head and neck oncologist because of the adverse effects of treatment on oral and pharyngeal function. By mimicking the common presentation of benign oral cavity pathology, delay in diagnosis is too frequent. Diagnosis at later stages results in low treatment outcomes and considerable costs to patients.^[2] The unique behaviour of these tumours requires vigilance and aggressive management to minimize the risk of loco-regional spread. Early detection and assessment of prognosis offers the best chance for long term survival and has the potential to improve treatment outcomes and make health care affordable.^[3]

Bioelectrical Impedance Analyzer derived Phase Angle is a cheap, non-invasive, easy and reproducible method with minimal intra and inter observer variability^[4] to assess malignancy by measuring altered tissue electrical properties.^[5] BIA works on the principle that electric current flows at different rates through the body

depending upon its composition. A low voltage current is applied and the lean tissue which consists essentially of electrolytes containing water conducts the electrical current whereas fat acts as an insulator.^[6] Impedance of the body is thus determined.^[7] Impedance is a measure of how current is slowed or stopped as it passes through the body. It has two components – Resistance (R) and Reactance (Xc). Resistance is the restriction to the flow of an electric current while reactance is the resistive effect produced by tissue interfaces & cell membrane.^[8] Reactance causes the current to lag behind the voltage creating a phase shift, which is quantified geometrically as the angular transformation of the ratio of resistance to reactance or the phase angle.^[9] Phase angle is the marker of cell and cell membrane structure and functional status. Low phase angle suggests cell death or decreased cell integrity while higher phase angle suggests healthy cell and cell membrane.^[10] A low phase angle has been associated with an impaired outcome in tumour diseases such as pancreatic cancer, colorectal cancer, lung cancer as well as in HIV/AIDS, liver cirrhosis, dialysis, pulmonary disease, bacteraemia and sepsis.^[10-16]

We know that cancer is now no longer seen as a single disease but a multifaceted disease comprised of distinct biological subtypes presenting a varied spectrum of clinical, pathological & molecular features with different prognostic and therapeutic implications. Malignant cells exhibit numerous anomalies in cell and its membrane which includes high aerobic lactate production, abnormal plasma membrane transport, and reduced number of cell junctions and appearance of new antigens. Shift in ion ratios (Na/K/Ca) occur within neoplastic cells resulting in abnormality in cell shape, cell movement and cell to cell communication. Alteration in cell membrane proteins play a major role in malignant behaviour.^[17] All these changes lead to disturbed cell physiology and thus altered tissue electrical properties. The altered tissue electrical properties documented in cancer patients occur even before the appearance of overt signs of cachexia.^[18] The primary objective of this study was to evaluate the association of BIA derived phase angle with TNM staging of carcinoma tongue. We took this study to establish or rule out BIA as a prognostic/ diagnostic indicator in malignancy.

II. Aim and Objective

To compare the Phase Angle in patients of biopsy proven anterior 2/3rd squamous cell carcinoma tongue and their matched control with the help of Bioelectric Impedance Analysis (BIA) to formulate some guidelines, if any.

III. Material and Methods

This prospective study was conducted on 74 patients (n=74) of histologically proven squamous cell carcinoma anterior 2/3rd tongue admitted in Department of General Surgery, Subharti Medical College, Meerut after taking clearance from ethical committee. 74 healthy volunteers (friends and relatives of patients) matched by age and sex was the control group. All of them were subjected to under mentioned inclusion and exclusion criteria. This study was done during July 2012 to October 2017 (64 months). A total of 74 male cases of histological proven anterior 2/3rd squamous cell carcinoma tongue with their matched controls were assessed for Phase Angle measurement by BIA BODY STAT QUAD SCAN 4000.

Inclusion Criteria

Patients admitted in Subharti Hospital with informed consent during July 2012 to October 2017 (64 months) with following prerequisites-

1. Biopsy proven cases of squamous cell carcinoma anterior 2/3rd tongue
2. Males aged 30-60 years
3. Patient not been treated prior for malignancy
4. Patient not suffering from diseases like Diabetes, hypertension, cirrhosis, hepatitis, HIV etc.

Exclusion Criteria

1. Patients who had received any prior surgical intervention for malignancy
2. Patients on Chemotherapy or Radiotherapy
3. Patients who were over hydrated or dehydrated
4. Cardiac patients with pacemakers
5. Patients with history suggestive of alcohol or drug abuse
6. Patient suffering from any medical condition affecting fluid and electrolyte balance.
7. Patients not giving consent.

IV. Procedure

Height was measured on a parallel plane stadiometer without shoes with a correction of 0.5cm. Weight was taken with minimal clothing on with correction of 0.1kg respectively. Hip circumference was measured at maximum posterior extension of buttocks while waist circumference was measured at a plane across iliac crest in standing position at end expiration. Two measurements were made at each site in rotational order with a 3rd measurement if the first two differed by more than 1cm. Subjects were instructed not to consume alcohol, coffee or do exercise 24 hours prior to test. They had to come with fasting of at least 4 hours. Following precautions were taken like subjects not wearing any metallic thing, no other electronic devices within 50 cm of BIA etc.

Subject lied supine on a non conducting couch with arms 30 degree apart from trunk and ankles at least 20 cm away. The parts where electrodes were to be placed were cleaned with alcohol. Bioelectric Impedance Analyzer BODY STAT QUAD SCAN 4000 was used. Red electrode was placed on the knuckles and black on the wrist next to ulna head in the right upper limb. In the right lower limb red lead was placed behind the toes and black in between the medial and lateral malleoli. BIA was done at 50, 100 & 200 kHz. All the readings were taken within 5 min of lying down. The Impedance of the body was determined. Impedance has two components Resistance (R) and Reactance (Xc). Resistance is the restriction to flow of an electric current while reactance causes current to lag behind the voltage creating a phase shift which is quantified geometrically as the angular transformation of the ratio of resistance to reactance or the phase angle. Phase Angle was calculated using following equation:

$$\text{Phase Angle} = (\text{Resistance}) / (\text{reactance}) * 180 / \pi.$$

All the patients proven to be cases of carcinoma tongue were staged according to American Joint Cancer Committee recommendations.

Phase angles of different stages were grouped accordingly. .

V. Statistical Analysis

We analysed the data with Graph pad prism software version 6.03 and Microsoft excel. Phase angle of test group was compared with that of control group by applying unpaired t test. One way ANOVA was applied to compare the mean phase angle of different stages.

VI. Results

We had 18 patients in Stage I contributing to 24.32% while there were no patients in Stage II. Stage III had a total of 18 cases contributing to 24.32% of total. Stage IVa had maximum number of cases amounting to 26 cases contributing 35.13% of total cases. Stage IVb had minimum number of cases, only 4 cases. Stage IVc had 8 cases making up 10.8%. Mean value of control and test group was calculated using unpaired t test. The mean value (\pm SEM) of control group was 5.659 (\pm 0.0713) while that of test group was 3.6432 (\pm 0.0548). The two differed significantly from each other with a p value of < 0.0001 which showed the significance of ****. (Table 1).

PATIENTS	CONTROL (n=74)	CASE (n=74)	P value	P value summary
PHASE ANGLE	5.659 \pm (0.0713)	3.643 \pm (0.0548)	<0.0001	****

Table 1: Phase Angle in Control and Patients of Carcinoma tongue.

Values are expressed as Mean \pm SEM. Analysis of data was done by unpaired t test using Graph Pad Prism Software Version 6.03. *(p<0.05), **s(p<0.01), *** (p<0.001), *****(p<0.0001). SEM: Standard Error Of Mean

In Stage I, the range of phase angle varied from 4.3 to 3.9. The mean value \pm SD was 4.10(0.122) Stage III had a maximum value of phase angle 3.9 while minimum value was 3.2 with a mean value \pm SD of 3.589 (0.257). The values of phase angle in Stage IVa varied from 3.8 to 3.2. The mean \pm SD calculated was 3.538 (0.180) for this stage. Stage IVb had highest value of 3.4 while least value of 3.3 with a mean value \pm SD of 3.350 (0.070). The mean \pm SD for stage IVc was 3.225 (0.125) with values ranging from 3.4 to 3.1 (Table-2).

Table 2: Mean Phase Angle in various stages of Carcinoma tongue.

Staging	PHASE ANGLE
I	4.10 (0.122)
III	3.589 (0.257)
IV a	3.538 (0.180)
IVb	3.35 (0.070)
IVc	3.225 (0.125)

Variables presented are Mean \pm SD.

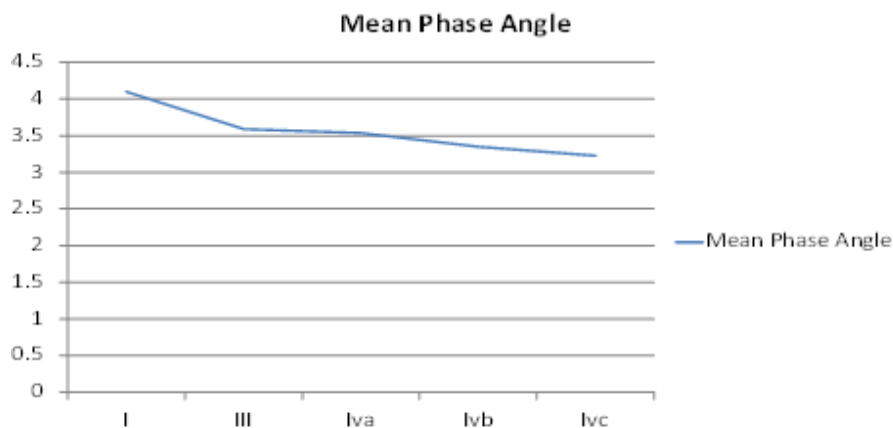
One way ANOVA was applied and the differences among means of all stages was statistically significant (****) with an f value of 21.38 and a p value < 0.0001. (Table 3) (Graph 1)

Stages of Malignancy	I	III	IVa	IVb	IVc	F value P value
Phase Angle	4.10 (0.122)	3.589 (0.257)	3.538 (0.180)	3.350 (0.070)	3.225 (0.125)	F= 21.38 P=<0.0001

TABLE: 3 Mean in different stages of carcinoma tongue

Variables are expressed as Mean ± SD. One Way ANOVA applied using Graph Pad Prism Version 6.03. *(p<0.05), ** (p<0.01), *** (p<0.001), **** (p<0.0001).

Mean Phase Angle in various stages of Carcinoma Tongue



Graph 1

VII. Discussion

The current study was undertaken to investigate if BIA derived phase angle differed significantly from the control group and whether phase angle of test group showed any pattern with staging of carcinoma tongue. This prospective case control study included comparison of a control group (n= 74) and a test group (n= 74) diagnosed as cases of squamous cell carcinoma tongue based on biopsy report. All cases of tongue malignancy were measured for phase angle but only those cases which fulfilled the inclusion criteria were included in the study.

In this study, we found that the phase angle was significantly lower in cases of carcinoma tongue and differed with their matched controls showing a significance level of ****. So any patient who comes with a lump or an ulcer in tongue with a reduced phase angle (after applying exclusion criteria mentioned in this study) should be investigated histopathologically on priority. One way ANOVA was applied and mean phase angles of all the stages were compared. Phase angle showed a decreasing trend as the staging of carcinoma tongue advances and also differed from each other showing a significance of ****. When compared to stage I, the phase angle in groups related to Stage III, IVa, IVb and IVc showed a significant decreasing trend. So as the disease got worsened the phase angle also reduced. So if two patients of carcinoma tongue come to us and one shows a much reduction in phase angle, it has been seen that the patient presented with higher staging and it indicates that disease is more advanced in this patient thus telling the prognosis. Further longitudinal studies are required to consolidate its role as a prognostic tool.

The phase angle reflects the status of cell & cell membrane. It can be considered as a global marker of health.^[19] The probable reason for the reduced phase angle in test group could be the altered and impaired cell structure and function. The neoplastic cells have impaired and reduced cell junctions, lost or new antigens, shift in ion ratios (Na, K, and Ca), abnormal plasma membrane transport, high aerobic lactate production and insertion of new proteins in cell membrane.^[17] Any change in tissue physiology should produce changes in the tissue electrical properties. BIA derived Impedance and phase angle detect changes in electrical properties.^[5] Reduced phase angle indicates a decreased ionic conduction with loss of dielectric mass. The observed impedance pattern which is reflected in form of phase angle is determined by dielectric properties of the cancer cells which appear even before the appearance of overt signs of cachexia. The standardized phase angle is an independent predictor for impaired functional and nutritional status and a better indicator of 6 month mortality than are malnutrition and disease severity in cancer.^[16]

There are few studies which support the role of phase angle in malignancy eg Gupta.D.et al; Implications for prognosis in advanced colorectal cancer and Davis MP et al; Phase angle changes during hydration & prognosis in advanced cancer.^[20, 21]

In a country like India, where we have limited resources and a large number of populations to diagnose and investigate, we can use phase angle as a screening tool in patients presenting with a growth or an ulcer in tongue. This study concludes that a reduced value of phase angle gives a clue for further investigation.

Key Message: Phase angle can be used as a diagnostic and prognostic tool in patients of carcinoma Tongue.

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