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RESEARCH ARTICLE

BIOELECTRIC IMPEDANCE PHASE ANGLE AS A DIAGNOSTIC AND PROGNOSTIC MARKER IN CARCINOMA TONGUE: A HOSPITAL-BASED STUDY

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Background: Malignancies of tongue represent one of the greatest management challenges for the head and neck oncologists because of the adverse effects of treatment on oral and pharyngeal functions. Diagnosis at later stages results in poor treatment outcomes and considerable costs to patients. Bioelectric impedance analysis (BIA)-derived phase angle offers an emerging opportunity to assess prognosis in these malignancies.
Aims and Objectives: To compare the phase angle between patients with squamous cell carcinoma of the tongue spanning anterior two-thirds and their matched controls with the help of BIA.
Materials and Methods: After obtaining clearance from ethics committee, we examined 37 male patients of histologically proven squamous cell carcinoma of the tongue and matched controls for phase angle by BIA Bodystat QuadScan 4000.
Results: In the control group, phase angle showed a mean ± SEM of 5.659 (0.0713) whereas in the test group it was 3.643(0.0548). One-way analysis of variance was applied and the results were found to be statistically significant.
Conclusion: This study showed that phase angle is a strong predictor of presence and severity of carcinoma of the tongue in patients.

INTRODUCTION

Oral cancer is a major health problem in the Indian subcontinent where it ranks among the top three types of cancer.[1] 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 the USA and less than 2 per 100,000 in the Middle East.[2] The tongue is the most common site for oral malignancy. Highest 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 oncologists because of the adverse effects of treatment on oral and pharyngeal functions. By mimicking the common presentation of benign oral cavity pathology, delay in diagnosis is too frequent. Diagnosis at later stages results in poor treatment outcomes and considerable costs to patients.[3] The unique behavior of these tumors requires vigilance and aggressive management to minimize the risk of locoregional 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.[4]

Bioelectrical impedance analyzer-derived phase angle is a cheap, noninvasive, easy and reproducible method with minimal intra- and inter-observer variability[5] to assess malignancy by measuring altered tissue electrical properties.[6] 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.[7] Impedance of the body is thus determined.[8] 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 (X_c). Resistance is the restriction to the flow of an electric current whereas reactance is the resistive effect

produced by tissue interfaces and cell membrane. [9] 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.[10] Phase angle is the marker of cell and cell membrane structure and functional status. Low phase angle suggests cell death or decreased cell integrity whereas high phase angle suggests healthy cell and cell membrane.[11] A low phase angle has been associated with an impaired outcome in tumor diseases such as pancreatic cancer, colorectal cancer, lung cancer as well as in HIV/AIDS, liver cirrhosis, dialysis, pulmonary disease, bacteremia, and sepsis.[11–17]

We know that cancer is now no longer seen as a single disease but a multifaceted disease comprising distinct biological subtypes, presenting a varied spectrum of clinical, pathological, and molecular features with different prognostic and therapeutic implications. Malignant cells show numerous anomalies in cell and its membrane, which include high aerobic lactate production, abnormal plasma membrane transport, reduced number of cell junctions, and appearance of new antigens. Shift in ion ratios (Na/K/Ca) occurs within neoplastic cells, resulting in abnormality in cell shape, cell movement, and cell-to-cell communication. Alteration in cell membrane proteins plays a major role in determining malignant behavior.[18] All these changes lead to disturbed cell physiology and thus altered tissue electrical properties. The altered tissue electrical properties reported in cancer patients occur even before the appearance of overt signs of cachexia.[19] The primary objective of this study was to evaluate the association of BIA-derived phase angle with tumor node metastasis (TNM) staging of carcinoma of the tongue. We undertook this study with a view to establish BIA as a prognostic/diagnostic indicator in malignancy.

MATERIALS AND METHODS

After obtaining clearance from ethics committee, we included 37 cases of histologically proven squamous cell carcinoma of the tongue spanning anterior two-thirds visiting the Department of Surgery in the study. Another 37 healthy volunteers (friends and relatives of the patients) matched by age and sex composed of the control group. All of them were subjected to the following inclusion and exclusion criteria:

Inclusion Criteria: (i) Biopsy-proven cases of squamous cell carcinoma of the tongue spanning anterior two-thirds; (ii) Men aged 30–60 years; (iii) Given informed consent; (iv) Absence of prior malignancy; (v) Absence of diseases such as diabetes, hypertension, cirrhosis, hepatitis, and HIV.

Exclusion Criteria: (i) Any prior surgery, chemotherapy, or radiotherapy; (ii) Overhydrated or dehydrated; (iii) Heart disease with pacemakers (iv) History of alcohol or drug abuse; (v) Any medical condition impacting fluid and electrolyte balance.

Height was measured on a parallel plane stadiometer without shoes with a correction of 0.5 cm. Weight was taken with minimal clothing on with correction of 0.1 kg. Hip circumference was measured at maximum posterior extension of buttocks whereas waist circumference was measured at a plane across iliac crest in standing position at end expiration. Two measurements were taken at each site in rotational order with a third measurement if the first two differed by more than 1 cm. Subjects were instructed not to consume alcohol or coffee, or do exercise 24 h before test. They had to come with fasting of at least 4 h. Precautions such as subjects not wearing any metallic thing and no other electronic devices within 50 cm of BIA were taken. Subject lied supine on a nonconducting couch with arms 30° 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 Bodystat QuadScan 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 performed at 50, 100, and 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 (X_c). Resistance is the restriction to flow of an electric current whereas 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:

$$\text{Phase Angle} = (\text{Resistance})/(\text{Reactance}) \times 180/\pi$$

All proven cases of carcinoma of the tongue were staged according to American Joint Cancer

Committee recommendations.

Phase angles of different stages were grouped accordingly and data were analyzed using GraphPad 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 analysis of variance (ANOVA) was applied to compare the mean phase angle of different stages.

RESULTS

Nine (24.32%) patients were assigned with each stage I and stage III, and 13 (35.13%) assigned with stage IVa; 2 assigned stage IVb, and 4 cases (10.8%) were assigned stage IVc. No patient was assigned stage II.

Table 1: Phase angle in control and patients with carcinoma tongue

	Control (*n* = 37)	Case (*n* = 37)	p-Value	p-Value summary
Phase Change	5.659 ± 0.0713	3.643 ± 0.0548	<0.0001	****

Values are expressed as mean ± SEM (Standard Error of Mean). Analysis of data was performed by unpaired t-test using GraphPad Prism software, version 6.03.
**p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001.*

Table 2: Mean phase angle in various stages of carcinoma tongue

Stage	Phase angle
I	4.10 (0.122)
III	3.589 (0.257)
IVa	3.538 (0.180)
IVb	3.35 (0.070)
IVc	3.225 (0.125)

Values are expressed as mean ± SD

Table 3: Mean of different stages of carcinoma tongue

	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

Variables are expressed as mean ± SD. One-way ANOVA applied using GraphPad Prism, version 6.03.
**p < 0.05; **p < 0.01; ***p <0.001; ****p < 0.0001.*

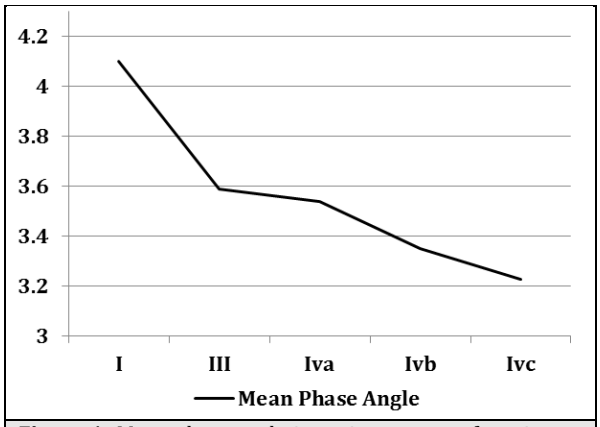

Figure 1: Mean phase angle in various stages of carcinoma tongue

Mean value of control and test groups was calculated using unpaired *t*-test. The mean ± SEM of the control group was 5.659 ± 0.0713 whereas that of test group was 3.6432 ± 0.0548. The two differed significantly from each other with a *p* value of <0.0001, which showed the significance of ****. In stage I, the range of phase angle varied from 4.3 to 3.9. The mean ± SD value was 4.10 ± 0.122. Patients assigned with stage III had a maximum phase angle of 3.9 whereas the minimum value was 3.2 with a mean ± SD of 3.589 ± 0.257. The values of phase angle in patients assigned stage IVa varied from 3.8 to 3.2. The mean ± SD calculated was 3.538 ± 0.180 for this stage. Stage IVb had highest value of 3.4 whereas the least value of 3.3 with a mean ± SD of 3.350±0.070. The mean ± SD for stage IVc was 3.225 ± 0.125 with values ranging from 3.4 to 3.1 (Table 2).

One-way ANOVA was used and the differences among means of all stages were found to be statistically significant (****) with an F-value of 21.38 and a *p*-value of < 0.0001.

DISCUSSION

This 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 of the tongue. This prospective case–control study included comparison of a control group (*n* = 37) and a test group (*n* = 37) diagnosed as cases of squamous cell carcinoma of the tongue based on biopsy report. All cases of tongue malignancy were measured for phase angle but only those that fulfilled the inclusion criteria were considered in the study.

In this study, we found that the phase angle was significantly lower in cases of carcinoma of the tongue and differed with their matched controls showing a significance level of ****. (So, any patient with a lump or an ulcer in tongue with a reduced phase angle (after applying exclusion criteria mentioned earlier) should be investigated histopathologically on priority.) One-way ANOVA was applied and mean phase angles of all the stages were compared, which showed a decreasing trend as the staging of carcinoma of the tongue advances and also differed from each other showing a significance of ****.. When compared to stage I, the phase angle in groups related to stages III, IVa, IVb, and IVc showed a significant decreasing trend. So, as the

disease worsened the phase angle also reduced. If a patient shows much reduction in phase angle, this could indicate higher staging and more advanced disease, thus showing the prognosis. Further longitudinal studies are required to consolidate its role as a prognostic tool.

The phase angle reflects the status of cell and cell membrane. It can be considered as a global marker of health.[9] 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.[18] Any change in tissue physiology should produce changes in the tissue electrical properties. BIA-derived impedance and phase angle detect changes in electrical properties.[6] Reduced phase angle indicates a decreased ionic conduction with loss of dielectric mass. The observed impedance pattern reflected in the 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 stronger indicator of 6-month mortality than are malnutrition and disease severity in patients with cancer.[17]

There are few studies that support the role of phase angle in malignancy, for example, study by Gupta[21] for implications for prognosis in advanced colorectal cancer and another by Davis[21] for phase angle changes during hydration and prognosis in advanced cancer.

CONCLUSION

In a country like India, where we have limited resources and a large population 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.

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