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Correlation of Salivary Ph, Blood Ph and Urine Ph in Potentially Malignant Disorders and Oral Cancer

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Abstract

Aim: It is noteworthy that many oral squamous cell carcinomas develop from potentially malignant disorders (PMD's). Correct diagnosis and timely treatment of PMD's may help prevent malignant transformation in oral lesions. For early detection of cancer, several studies have led to discovery of many cancer biomarkers, including Salivary, Blood & Urinary markers. The concentration of H+ in saliva, blood and urine is among the most tightly regulated variables in human physiology. Acidic pH is toxic to many cells, including tumors. The aim of the study is to assess and compare salivary pH, blood pH and urinary pH in patients with Potentially Malignant Disorders, Oral cancer & control groups.

Materials & Methods: Unstimulated saliva, venous blood, and urine samples of 30 patients with potentially malignant disorder/oral cancer and of 30 control patients were collected and their pH values were evaluated and compared. The data collected was subjected to statistical analysis.

Results: The pH values of saliva were reduced significantly (P = 0.002) in potentially malignant disorders and oral cancer when compared with controls. Whereas blood pH and urinary pH showed insignificant results with p values of 0.969 and 0.547 respectively.

Conclusion: Alterations in Salivary pH have a role in diagnosing Potentially Malignant Disorders & Oral cancer at an early stage.

Keywords: Oral Cancer, Potentially Malignant Disorders, Salivary pH, Blood pH, Urine pH

Introduction

Oral cancer, the sixth most common human cancer is a serious and growing problem with a mortality rate of approximately 50%. The high morbidity can be attributed to the delay in diagnosis of the disease[1,2]. Following were identified as PMD's by the World Health Organization's working group on Oral Cancer: Leukoplakia, Erythroplakia, Oral Lichen planus, Oral submucous fibrosis etc[3,4]. Several studies have led to the discovery of cancer biomarkers, including Salivary biomarkers[5,6].

Saliva is a clinically informative, biological fluid (biofluid) that is useful for novel approaches to prognosis, laboratory or clinical diagnosis and management of patients with both oral and systemic diseases[7,8]. Most of the potential salivary biomarkers include salivary pH levels and salivary proteins like amylase and lysozyme[9,10]. The concentration of H+ in blood plasma is among the most tightly regulated variables in human physiology. Studies have shown a dose - response relationship in bladder cancer risk with urinary acidity[16,17]. Acidic pH is toxic to many cells, including tumors. Management of tumor pH are important in raising drug efficacy and in preventing metastasis[11].

The aim of this study was to estimate the salivary pH, blood pH and urine pH in potentially malignant disorders and oral cancer compared to the controls for the management of tumor pH which helps in raising drug efficacy and in preventing metastasis.

Materials & Methods

The study protocol was approved by the Institutional Ethical Review Board and the study was conducted in the department of Oral Medicine and Radiology at Panineeya Mahavidyalaya Institute of Dental Sciences and Research Institute, MNJ Institute of oncology and regional cancer centre, KIIMS-BiBi Regional Cancer Institute. Before initiating the study a written informed consent was obtained from the patients who were willing to participate in the study.Study sample was divided into two groups. Group A consisted of 30 Patients who has potentially malignant disorders or oral carcinomas. Group B consisted of control group of 30 pateints without any lesion who have come for regular dental check up.

Inclusion Criteria

Patients who were diagnosed clinically and histo-pathologically with premalignant and malignant conditions and willing for the study between the age group of 25 to 70 years and both genders were included in the study.

Exclusion Criteria

Patients who were on medication for systemic diseases which can alter the pH of body fluids, patients with malignant lesions who were already on chemotherapy and radiotherapy and patients suffering with carcinomas other than oral cavity were excluded in the study.

Method

Unstimulated saliva was collected for 15 minutes one hour prior to any intake of food items. Sample collected was stored at -4 degree centigrade. Blood sample was collected under sterilized condition with 25-gauge needle syringe. Urine sample was obtained from the patient in 5 cc wide mouth container. pH was estimated in all the samples by using pH meter.**[Figure 1]**

Fig 1: pH Meter

Statistical Analysis

Data obtained was processed and was subjected to statistical analysis by SPSS version 22.0 software. The comparison between two groups was done by unpaired t-test/Mann Whitney U test for continuous data and the association between variables was done by chi-square test. The relation between variables was done by Karl Pearson's correlation test. All p-values less than 0.05 were considered statistically significant.

Results

There was statistically significant (p value- 0.002) decrease in salivary pH in PMD & OC patients compared with controls. There was no statistically significant difference between control and PMD & OC for the parameters of Blood pH and Urine pH where the p-values are 0.969 and 0.547 respectively. [Table 1]

Parameter	*Groups*	*N*	*Range*	*Mean*	*SD*	*P-value*
Salivary pH	*Control*	30	5 to 8.5	6.62	0.75	*0.002*[a]
	PMD&OC	30	5 to 7.5	6.05	0.60	
Blood pH	*Control*	30	7.3 to 7.4	7.34	0.04	0.969[b]
	PMD&OC	30	7.2 to 7.4	7.33	0.07	
Urinary pH	*Control*	30	4.4 to 7.5	5.87	0.77	0.547[a]
	PMD&OC	30	5 to 7.5	5.98	0.66	

Table 1:Comparison between control and PMD & OC for the parameters salivary pH, Blood Ph, Urinary pH.

There was a significant decrease in salivary pH in PMD & OC females compared to the females in control group with a p value of 0.027. The blood pH and urinary pH were found to be statistically insignificant between the female subjects of both groups with p-values of 0.465 and 0.291 respectively.[Table 2]

Parameter	*Groups*	*N*	*Range*	*Mean*	*SD*	*P-value*
Salivary pH	*Control*	22	5 to 8	6.56	0.76	*0.027*
	PMD & OC	12	5 to 6.8	6.00	0.49	
Blood pH	*Control*	22	7.3 to 7.4	7.34	0.04	0.465
	PMD & OC	12	7.3 to 7.4	7.35	0.05	
Urinary pH	*Control*	22	4.6 to 7	5.77	0.68	0.291
	PMD & OC	12	5 to 7	6.03	0.60	

Table -2: Comparison between control and PMD & OC for the parameters salivary pH, Blood Ph, Urinary pH in female subjects.

There was a significant decrease in the salivary pH in PMD & OC compared to controls in male subjects with a p value of 0.026. There was statistical insignificance between PMD/OC and control in blood pH and urinary pH among the males with p-values of 0.538 and 0.615 respectively. [Table 3]

Parameter	*Groups*	*N*	*Range*	*Mean*	*SD*	*P-value*
Salivary pH	*Control*	8	6 to 8.5	6.80	0.77	*0.026*
	PMD & OC	18	5 to 7.5	6.09	0.68	
Blood pH	*Control*	8	7.3 to 7.4	7.34	0.05	0.538
	PMD & OC	18	7.2 to 7.4	7.32	0.07	
Urinary pH	*Control*	8	4.4 to 7.5	6.13	1.00	0.615
	PMD & OC	18	5.0 to 7.5	5.95	0.72	

Table 3: Comparison between control and PMD & OC for the parameters salivary pH, Blood Ph, Urinary pH in male subjects

Karl Pearson's correlation test revealed no significant correlation between salivary, blood and urinary pH among the PMD, OC patients and controls.[Table 4]

Control		SALIVARY pH	BLOOD pH	URINARY pH
SALIVARY pH	Pearson Correlation ®		-0.067	-0.016
	p-value		0.727	0.934
	N	30	30	30
PMD		SALIVARY pH	BLOOD pH	URINARY pH
SALIVARY pH	Pearson Correlation		-0.196	0.37
	p-value		0.521	0.214
	N	13	13	13
OC		SALIVARY pH	BLOOD pH	URINARY pH
SALIVARY pH	Pearson Correlation		0.268	-0.338
	p-value		0.299	0.184
	N	17	17	17

Table 4: The relation between groups for the parameters salivary pH, Blood Ph, Urinary pH

Discussion

For early detection of cancer, studies have led to discovery of many cancer biomarkers, including salivary, blood and urine biomarkers.[12,13] Over the past decade, salivary diagnostics have received increasing attention as a growing number of high-impact systemic diseases and physiological conditions were shown to be accurately reflected by the composition of saliva. Most of these efforts have concentrated on technological advancement and assay development. The improved accuracy of

genomic and proteomic biomarker discovery technologies is turning salivary diagnostics into a clinical and commercial reality. The miniaturization technology known as “lab-on-a-chip” provides a new avenue for point-of-care diagnostics. Furthermore, because miniaturization allows diagnosis to be performed outside of the laboratory, such as in the home, this new technology may further enhance the healthcare delivery, reduce health disparities. New technologies in association with the saliva-based approach, which is painless, inexpensive, easier, and safer than approaches based on serum or urine, can significantly impact molecular diagnostics.[14,15]

Saliva is a complex fluid rich in organic and inorganic constituents.[16,17] The salivary pH could be defined as the negative logarithm of the hydrogen ions concentration. It plays a significant role in the equilibrium between the calcium phosphate of the tooth and the surrounding liquid phase[17].The use of tobacco products elicits various oral manifestations starting from simple attrition of teeth to malignant oral lesions and carcinomas.[18]

According to Keiichi Morishita in his Hidden Truth of Cancer, If the blood develops a more acidic condition, then our body inevitably deposits these excess acidic substances, so that the blood will not be able to maintain an alkaline condition, which causes the cells to become acidic and lowers in oxygen. In other words, instead of dying - as normal cells do in an acid environment - some cells survive by becoming abnormal cells. These abnormal cells are called malignant cells.[19,20]

The study was carried out to estimate and correlate the salivary pH, blood pH and urine pH in potentially malignant disorders and oral cancer. Our study included a total of 60 participants, of which 30 were diagnosed with potentially malignant disorders like oral submucous fibrosis, lichen planus, leukoplakia and histologically diagnosed oral carcinomas and 30 without any lesion, who came for regular dental check up (controls).

When Salivary pH was compared between controls, potentially malignant disorders and oral cancer patients, a significant difference was found between groups (p=.008). Lowest salivary pH was observed in oral cancer group followed by potentially malignant group and control group. This supports the study conducted by Ramya et al where they found lower salivary pH values in cancer patients group. According to them, the decrease in pH levels in cancer patients was attributed to uncontrolled growth of the tumor cells, which create an imbalance in the ratio of demand and supply of the nutrition to the tumor cells. As a result of high uptake of glucose by the tumor cells and subsequent anaerobic glycolysis, it leads to lactic acid production, which may be the reason for the acidic environment observed in the oral cavity of cancer patients.[1]

The mean blood pH was found to be reduced in patients with potentially malignant disorders (7.344), oral cancer (7.318) when compared to controls (7.335). But the difference was not significant. Ohishi et al examined the effect of mild hyperthermia on venous blood pH in six cancer patients. These patients showed good physical conditions and improved clinical data. The present data suggest that mild hyperthermia is a useful method to improve circulation failure, physical condition and clinical data.[21]thus we can assume that pH has a major role in management of cancer patients.

Studies have hypothesised that acidic environment has a role in tumor metastases, recurrence, and prognosis in some cancer patients. According to them, the underlying molecular mechanism relating to these clinical contributions is that lactate from tumor cells contributes to their immune escape. The high lactate production is thought to be due to the “Warburg effect”, a well-accepted

theory that says that tumors tend to produce lactate by using the anaerobic glycolytic pathway, even in the presence of sufficient oxygen.[22]

Urine contains growth factors that enhance the proliferation and tumorigenicity of the bladder epithelium. In addition, urine pH and numerous components of the urine, such as calcium, protein, can markedly alter the urinary tract effects of many of these carcinogens, either directly or indirectly.[23,24] The mean urine pH was found to be reduced in patients with potentially malignant disorders and oral cancer when compared to controls. But the difference was not significant (p= 0.821). Alguacil et al found that a consistently acidic urine pH (6.0) was associated with an increased risk of bladder cancer.[25]

There has been considerable interest over the application of saliva-based diagnostics for oral diseases. A study in a larger sample and patients with cancer of oral cavity and also in patients with cancer involving other parts of body are to be carried out. The present study concluded that altered pH values in saliva can be considered as one of screening diagnostic modality in potentially malignant disorder and oral cancer patients.

Conclusion

With all the observation and studies, we aimed at changes in microenvironment of oral cavity influencing other bodily fluids like blood and urine for diagnostic and prognostic purposes. There is a big lacuna in the present scenario of evidence based dentistry which correlates the role of new critical parameters like salivary pH in detecting the oral cancer. Managing a disease, especially in the early stage, may dramatically reduce the severity of its impact on the patient's life, or prevent and/or delay subsequent complications.

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