Salivary Zinc level and Taste Detection Thresholds in Hypertensive Patients on Amlodipine and on Losartan (A Comparative Study)

Yosor M. Akram[1], Taghreed F. Zaidan[2], Zaid M Akram[3], Omar A. Abed Alsattar[4]

[1]M.Sc.student, [2]Professor, Department of Oral Diagnosis, Collage of Dentistry, University of Baghdad, [3]Lecturer, Al-Rafiddain University College, [4]High Diploma Degree in Periodontics, Al-Ameriya Specialized Center for Dentistry, Baghdad Medical Department /AlKarkh , Ministry of health.

Abstract

High blood pressure (hypertension) is one of greatest risk factors for cardiovascular disease,which is a remarkable cause of morbidity and mortality worldwide. The outcome of hypertension (HTN) and cardiovascular disease (CVD) is influenced by a wide variation of risk factors like use of tobacco; excessive alcohol consumption; unhealthy diet, few physical activity ,overweight and obesity; high blood glucose, and abnormal blood lipids. The objectives of this study were to evaluate taste detection thresholds (of four basic tastes) of hypertensive patients on Amlodipine 5 mg and on Losartan 50 mg. And to estimate Zinc level in saliva of those patients and compare it with control subjects. A total of 90 subjects were incorporated in this study they were divided into three groups: 1-Thirty patients on Amlodipine (5mg) 2-Thirty patients on Losartan (50mg) and 3- Thirty healthy control subjects. Unstimulated whole saliva was collected from all subjects including in this study. Volume of 5 ml of each taste gradient solution,was offered to the participants. The samples were subjected to biomechanical analysis to estimate zinc level by using the atomic absorption spectrophotometer.The result showed that the taste detection threshold of sucrose and sault were significantly higher in patients on Amlodipine and on Losartan treatment than in control subjects. While the taste detection threshold of sour and bitter showed no significant differences between the study groups. Also there is un alteration in salivary Zinc, Zinc in patients on Amlodipine and on Losartan was significantly lower compared to control group.

Keywords: *Taste Detection Thresholds, Hypertensive, Amlodipine, Losartan, Zinc*

Introduction

Hypertension is often called a silent killer since frequently there are no clear symptoms. Initial signs of hypertension may be non-specific (headaches, excessive irritability, insomnia, decreased tolerance to exercise, palpitations and flushing of the head, neck and chest) and thus confusing[1]. Hypertension has lately been reaffirmed as the major single risk factor contributing to world death rates[2]. Besides , control of hypertension is one of the most cost-effective process to decrease early cardiovascular morbidity and mortality[3]. The national institute for health and care excellence(NICE) recommended that management of high blood pressure with any of many classes of common medication is cost saving compared with providing of no medication .The aims of management of hypertension is to control arterial pressure, prevent end-organ damage (cardiovascular ,cerebrovascular, and renal), and to decrease the chance of premature death[4].

Classification of drugs may be done by mechanism or site of action (therapeutic british hypertension society, 2014). In each class, there are numerous drugs with variation in structure and pharmacology resulting in alteration in therapeutic and side-effects[5].

Amlodipine is an oral dihydropyridine calcium channel blocker. Compared to nifedipine and other medications in the dihydropyridine class, amlodipine

Corresponding author:-
Yosor Mustafa Akram, general practice dentist in Ministry of health, Baghdad/Iraq ,
E-mail: yosor.m.akram@gmail.com

has the longest half-life at 30 to 50 hours. The advantage of such a long half-life is the ability to have once-daily dosing. Amlodipine (dihydropyridines) has been described to be an efficient antihypertensive medication related with regression of left ventricular hypertrophy and vascular hypertrophy, the antiatherogenic and the remodeling effects[6].

Losartan is an angiotensin II receptor antagonist (AIIRA) with antihypertensive action due mainly to selective blockade of (AT1) receptors and as the consequence reduced the effect of angiotensin II in elevation of blood pressure. Losartan use in the management of hypertension and heart failure , especially in patients who develop cough with the use of Angiotensin converting enzyme (ACE) inhibitors, additionally it is used in patients with left ventricular hypertrophy to reduce the risk of stroke, and also used in the management of diabetic nephropathy, and has been tried in management of myocardial infarction[7]. Peak plasma concentrations of losartan are achieved within one hour of oral administration the half-life of Losartan 1.5–2.5 hours[8].

Taste is an important protective sense, progressed to manage the intake of food and help in the avoidance of poison. Genetic considered as the principal determinants of taste threshold, and taste thresholds do not differ significantly from day to day. This has lead to the idea of "non-tasters" and "supertasters''[9], in which the taste threshold is linked to the haplotype(a combination of alleles for different genes and tend to be inherited together) of specific receptors[10]. Taste disturbances may arise secondary to autoimmune disease, inflammation, imbalance of hormone, nerve-related damage, psychological problems like in anorexia, medication therapy or malignancy; they may also occur as a consequence of natural aging[11]. Zinc is an essential trace element and is found in tissues throughout the body, reaching iron in its relative abundance[12]. The body of human carry about 2g of zinc, approximately 60% of which is found in muscle tissue, 30% in bone and 5% in skin[13].

Aims and Objectives

1- To Evaluate taste detection thresholds (of four basic tastes) of hypertensive patients on Amlodipine (5 mg) and on Losartan (50 mg).

2- To estimate Zinc level in saliva of those patients and compare it with control subjects.

Materials and Method

This case control study was conducted in the period from February 2019 to May 2019. After approval from Ministry of Health and College of Dentistry University of Baghdad by the scientific committee. A total of 90 subjects were incorporated in this study, they were divided into three groups: 1- Thirty patients on Amlodipine 5mg. 2- Thirty patients on Losartan 50mg. 3- thirty healthy control subjects.

Inclusion criteria: All patients presented with hypertension and they were under antihypertensive monotherapy for at least 8 months .The antihypertensive medications that used by the patients are: Amlodipine and Losartan.

Exclusion criteria: hypertensive patient taking combination of antihypertensive medications, Diabetes mellitus, Renal failure, smoking, patients with history of radiotherapy in the head and neck region ,and history of chemotherapeutic treatment in the last 3 months.

Each taste gradient consisted of 15 solution ,from 1.5 to 15.5 mmol (in 1 mmol increments) for sucrose, from 1-78 mmol (in 5.5 mmol increments) for sodium chloride , from 48 -720 µmol (in 48 µmol increments)for citric acid , and from 89-117 mmol (in 2mmol increments) for urea[14]. Taste solution were Prepared by calculation the amount of taste substance in grams dissolved in deionized water for recommended concentration according to weight (g)= molecular weight(g/mole) x concentration(M) x volume(ml)/1000[15]. The concentrations of solutions used are shown in table (1). The sip and spit method was used, the taste solution were swirled around in the mouth briefly and expectorated into an empty cup[16].

Table (1): The concentration of taste solutions used (Amerine and Pangborn, 1965)[14]

Sucrose mmol/L	Sodium chloride mmol/L	Citric acid µmol/L	Urea mmol /L
1.5	1	48	89
2.5	6.5	96	91
3.5	12	144	93
4.5	17.5	192	95
5.5	23	240	97
6.5	28.5	288	99
7.5	34	336	101
8.5	39.5	384	103
9.5	45	432	105
10.5	50.5	480	107
11.5	56	528	109
12.5	61.5	567	111
13.5	67	624	113
14.5	72.5	672	115
15.5	78	720	117

Statistical Analysis

The statistical package for the social sciences (SPSS) was used for data input and analysis. The statistical significance of difference in mean between more than two groups was assessed using the ANOVA model. When statistically significant difference was shown by the use of ANOVA, further exploration of the statistical significance of difference in mean between each two groups was assessed by post –hoc multiple comparison Least Significant Difference(LSD) test.

Results

This study showed that the mean and standard deviation of the taste detection threshold of sucrose (sweetness) of patients on Amlodipine was 14.16± 2.48 mmol/l , and those on Losartan treatment was 12.76±3.20 mmol/l. For the control subjects was 8.16 ±2.48 mmol/l. It has been found that the taste detection threshold of sweet showed significant difference ($p<0.001$) using ANOVA test and was highest among patients on Amlodipine (Table 2).Continuing analysis with (LSD) test showed that the taste detection thresholds of sweetness was significantly higher in patients on Amlodipine and on Losartan treatment than in control

subjects (p<0.00 1) but no significant difference has been found between patients on Losartan and patients on Amlodipine (Table 3).

The mean and standard deviation of the detection threshold of salty taste of patients on Amlodipine patients was 52.90± 12.03 mmol/l , and on Losartan treatment was 55.83± 14.94 mmol/l , while in control subjects was 32.11±21.66 mmol/l. It has been shown that the detection threshold of salt was significantly higher in patients on Amlodipine and Losartan treatment than that in the control subjects (Table 2) .Continuing analysis with (LSD) test, showed that the taste detection thresholds of salt in patients on Amlodipine was significantly higher than that of control subjects. And the taste detection thresholds of salt in patients on Losartan was significantly higher than that of control subjects , but no significant differences was found between patients on Amlodipine and patients on Losartan (Table 3).

For the sour taste, the results showed that the mean and standard deviation of the detection threshold for citric acid in Amlodipine patients was 473.43±183.91 µmol/l and of patients on Losartan treatment was 453.23 ±175.59 µmol/l, while in control subjects the detection threshold for citric acid (sourness) was 515.46±192.34 µmol/l (Table 2). Statistical analysis showed no significant differences between the study groups.

For the bitter taste, it has been shown that the mean and standard deviation of urea (bitterness) in patients on Amlodipine patients was 91.75± 21.09 mmol/l, and for Losartan treatment was 85.00 ± 26.32 mmol/l, while for control subjects was 92.20±17.51 mmol/l (Table 2).No significant differences was found between the study groups.

Table (2):- The mean and standard deviations of the taste detection threshold of the four tastes in study groups

Group	Sweet		Salt		Sour		Bitter	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Amlodipine	14.16	2.48	52.90	12.03	473.43	183.91	91.75	21.09
Losartan	12.76	3.20	55.83	14.94	453.23	175.59	85.00	26.32
Control	8.16	2.48	32.11	21.66	515.46	192.34	92.20	17.51
P. value	0.00** HS		0.00** HS		0.41 NS		0.36 NS	

All units in mmol/L except for sourness in µmol/l

** HS:Highly significant p<0.001 NS: - None significant p> 0.05

Table (3): - Multiple comparisons using LSD among study groups

Variables	Subgroups	Subgroups	Std. Error	P. Vlue
Sweet	Amlodipine	Losartan	.70857	0.051
		Control	.70857	.000 HS
	Losartan	Control	.70857	.000 HS
Salt	Amlodipine	Losartan	4.3147	0.498
		Control	4.3147	.000 HS
	Losartan	Control	4.3147	.000 HS

** HS: Highly significant p<0.001

For salivary zinc the mean and standard deviation of patient on Amlodipine and Losartan treatment and for the control subjects showed in Table 4.The statistical analysis using ANOVA test demonstrated that salivary Zinc showed significant differences ($p<0.001$) between the control group and the two study groups. Continuing analysis with (LSD) test showed that the mean of salivary zinc in patients on Amlodipine and in patients on Losartan was significantly lower compared to control group ($p<0.001$) .while no significant difference between the mean of salivary zinc in patients on Amlodipine and on Losartan ($p> 0.05$)(Table5).

Table (4):-The mean and standard deviations of salivary Zinc in study groups with ANOVA

Group		**Zn µg /dl**
Amilodipine	Mean	3.29
	SD	0.71
Losartan	Mean	3.45
	SD	0.75
Control	Mean	5.93
	SD	1.03
P-value		.000 HS

HS:-Highly significant at $p<0.001$

Table (5): Multiple comparison of Zinc using LSD among the study groups

Variables	**Subgroups**	**Subgroups**	**Std. Error**	**P. Vlue**
Zn	Amlodipine	Losartan	0.2191	0.476
		Control	0.2191	0.000 HS
	Losartan	control	0.2191	0.000 HS

HS:-Highly significant at $p<0.001$

Discussion

Hypertension (HTN or HT), also known as high blood pressure , is define as a long-term medical condition in which arterial blood pressure is elevated persistently[17].

Sweet detection thresholds of sucrose (sweetness) of patients on Amlodipine and those on Losartan treatment were significantly higher than that of control subjects. Salt detection threshold in patients on Amlodipine and on Losartan treatment which were significantly higher than that of control subjects. For the sour detection threshold, it was lower in patients on Amlodipine and Losartan treatments than the control subjects but it did not reach the significant level. For the bitter detection thresholds it showed no significant differences between the study groups. This result was agree with Tsuruoka *et al.*, 2005 ,who found that Losartan induced taste disturbances and they found that the taste disturbance by the Losartan and Perindopril (ACI-groups) medications at the dosages used was similar in quality and quantity. But disagree with Tsuruoka *et al., (*2005) who stated that Losartan-induced taste disturbances appear to be larger for "bitterness" and "sourness" than "salt" and "sweetness"[18]. It has been hypothesized that a prominent underlying pharmacological mechanism, may explain taste disorders as a class effect of Angiotensin receptor blocker (ARBs). Taste receptors are seven-transmembrane domain G protein-coupled receptors. Angiotensin II receptors belong to the same type of receptor .The sweet and bitter receptors on taste cells are coupled with G-proteins, where G-protein coupling and uncoupling results in taste on and off, respectively ARBs are secreted into saliva, binding receptors of taste and thereby distorting the tastes of sweet and bitter ,Salt and sour tastes may be disrupted by ARBs ion channels plugging or obstructing (salt taste via amiloride-sensitive epithelial Na channels, and sour taste via amiloride-sensitive epithelial Na channels and H+-activated cation channels) found on taste cells[19]. This result was disagree with Kim et al .,(2017) who reported that salt-taste thresholds did not significantly differ between the control and hypertension groups[20].

The result showed that salivary Zinc of patients on Amlodipine and for patients on Losartan treatment were highly significantly decreased than that of control subjects. This result agree with (Korean *et al.,* 2005) who found that Losartan treatment result in Zn depletion, mediated by an increase in urinary Zinc excretion[21].

This result was also agree with (Ifor, 1989) who found that there is a decrease in the level of salivary Zinc level in hypertensive patient[22].

Conclusions

Amlodipine and Losartan can affect taste detection thresholds of sweet, salt in such a way that they were detected taste with high concentrations of taste solutions, but sour and bitter taste was not affected. And Zinc in saliva was decreased significantly by treatment with these medication.

Conflict of Interest We declare that we have no conflicts of interest.

Human and Animal Rights All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee.

Informed consent Informed consent was obtained from all individual patients ,including in this study

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