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COMPARISON OF ACUTE EFFECTS OF SUCRALOSE, ASPARTAME AND ACESULFAME POTASSIUM ON PULSE, BLOOD PRESSURE, AND BLOOD GLUCOSE LEVELS IN YOUNG HEALTHY ADULTS

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ABSTRACT

Background: The use of non-nutritive sweeteners (NNSs) have become increasingly popular, so their health benefits and potential adverse effects should be evaluated. **Methodology:** This nonrandomized case-control comparative study was done at Mohi ud-Din Islamic Medical College on 200 healthy undergraduate medical students in October 2017 after approval from ethical committee. The participants were equally divided into groups A, B, C and D. The control group A was given 100 gm cellulose while participants of group B, C and D were given 0.36 gm (5 mg/kg) sucralose, 10.8 gm (150 mg/kg) aspartame and 3.24 gm (45 mg/kg) acesulfame potassium respectively in a glass of 180 ml water. The arterial pulse, systolic and diastolic pressures were measured at 0, 30, 60, 90 and 120 minutes. The random blood glucose levels were checked at 0 and 120 minutes in all the participants. **Results:** The random blood glucose levels showed a non-significant difference ($p>0.05$) at 0 and 120 minutes within and

between all the study groups. A significant difference ($p<0.05$) regarding the pulse rate at 60, 90 and 120 minutes was noticed between participants of group A and B with that of group C and D. The systolic pressure in participants of group A showed a significant difference ($p<0.05$) with that of group C and D at 60, 90 and 120 minutes, while the diastolic pressure at 0, 30, 60, 90 and 120 minutes between and within the groups was found to be non-significant ($p>0.05$). **Conclusion:** The artificial sweetener use showed cardio-metabolic health effects which require further evaluation, however, the effects on glucose metabolism is non-significant. **Objectives:** To see the acute effects of non-nutritive sweeteners on blood pressure, pulse and blood glucose levels in young healthy individuals.

KEYWORDS: Non-nutritive-sweeteners, Pulse, Blood-pressure, Glucose.

INTRODUCTION

The major contributing factor to rising obesity epidemic is excess consumption of energy-dense foods and reduced physical activity.[1] while epigenetic changes, alterations of microbiome, drugs, psychological issues, endocrine disruptors, chronic sleep deprivation, use of artificial sweeteners and soft drinks also play major role in obesity.[2]

The health issues related to obesity, like maturity onset diabetes mellitus (type 2), hypertension and heart diseases are not only seen in older but also increasing in the youth. Most foods marketed towards children are sugar-laden, a common diet component and one of the major contributing factors to obesity and dental diseases both in children and adults.[3]

Only in US billions of dollars are required to manage morbidity and mortality related to obesity, which can be managed simply by dietary interventions. Numerous diets amidst quick weight loss; one such product group is non-nutritive sweeteners (NNS).[4]

Nonnutritive or artificial sweeteners are used, instead of sugars, to flavor and sweeten foods, beverages and the products used in oral care and in medications. They contain few or no calories or nutrients and derived from plants, herbs, or even sugar itself. They have a greater intensity of sweetness compared with sugar, so smaller quantities are needed in foods and beverages. Currently NNS used as sweetener in food include sucralose, aspartame, saccharin, acesulfame potassium, neotame, advantame, steviol glycosides, and Luo han guo extract. These have been recognized safe for use in food by the US Food and Drug Administration (FDA).[5]

The NNSs effect energy balance and metabolism through strong activation of the heterodimeric (T1R1 + T1R3) oral and extra-oral sweet taste receptors and effect hormonal secretion, cognitive actions (like taste perception, reward learning and memory) and gut microbiota.[6]

The sucralose was discovered during a collaborative research project of the Tate & Lyle Company and the Queen Elizabeth College in 1980. Sucralose, a substituted chlorinated disaccharide with a molecular weight of 400, is described as 4, 10, 6'-trichlorogalactosucrose. On weight for weight basis, it is 600 times sweeter than that of sugar and is stable at high temperature and low pH. The hydrolysis products (4-CG, 1-6 DCF) are more rapidly absorbed than sucralose: 1, 6-DCF undergoes rapid conjugation with glutathione and eliminated in the urine, while 4-CG is excreted intact in the urine. The FDA approved sucralose in 1998 and was used as a non-caloric high intensity sweetener in foods and beverages.[7]

Aspartame, an odorless white crystalline powder, derived from aspartic acid and phenylalanine, was discovered by James M. Schlatter while working on an anti-ulcer drug. It is about 200 times sweeter than sugar and is used in frozen desserts, gelatins, beverages and chewing gum. On cooking or when metabolized, it breaks down into its constituent amino acids but is stable in acidic condition.[8] Aspartame is one of the most widely tested food ingredients to date but had shown cancer, neurological as well as psychiatric side effects by various researchers.[9]

Currently it is found safe for consumption by regulatory bodies like UK Food Standards Agency,[10] European Food Safety Authority (EFSA).[11]

https://en.wikipedia.org/wiki/Sugar_substitute - cite_note-19and by the Health Canada.[12]

Acesulfame potassium (C4H4KNO4S), a heat stable, white crystalline powder with molecular weight of 201.24 g/mol. is as sweet as aspartame, but bitter aftertaste. Acesulfame potassium is often blended with sucralose or aspartame (Ovaltine, carbonated drinks, pharmaceutical products) and is widely used in diet, baking, protein shakes and chewable as well as in liquid pharmaceutical products.[13] Its absorption is by interaction of S-O double bond with metal hydroxide layers, degrade to acetoacetamide and excreted by the kidneys. Acesulfame potassium aids patients with type 1 diabetes but labeled as anticonvulsants.

https://en.wikipedia.org/wiki/Acesulfame_potassium - cite_note-Talevi,_Alan_2012-12. The FDA expanded its approval for use in beverages in 1998 and as a general sweetener in 2003.[14]

The use of artificial sweeteners increase the risk for metabolic syndrome, type 2 diabetes, hypertension and cardiovascular disease.[15] Presently, no definitive data regarding the acute effects of NNS related to cardiometabolic effects is available, though the FDA had endorsed the safety of these additives. Our study was aimed to see the acute effects of different non-nutritive sweeteners on blood pressure, pulse and blood glucose levels in healthy individuals.

MATERIAL AND METHOD

This nonrandomized case control comparative study with done at Mohi ud-Din Islamic Medical College AJK undergraduate medical students in October 2017, after approval from institutional ethical committee and consent of inducted students after explaining the procedure. A total of 200 students of class 2019 and 2020 were selected non-randomly and were equally divided into 4 groups A, B, C and D (n-50). Participants with history of illness related to heart, taking medication for hypertension, depression, anxiety, or having any vascular diseases were excluded from the study.

Group A was taken as control, while students of group B, C and D were taken as cases. Before collection of data all participants were seated in a hall for duration of two hours to explain the methodology and to remove effect of any confounding factor on arterial pulse, systolic and diastolic blood pressure (mental or physical stress).

At 0 times, the arterial pulse rate from radial artery, systolic and diastolic blood pressure from brachial artery were measured in all the participants. The participants of group B, C and D were given 0.36gm (5mg/kg) sucralose, 10.8 gm (150mg/kg) aspartame and 3.24gm (45 mg/kg) acesulfame potassium respectively with a glass of 180 ml of water, the dose of these NNSs has 200 time more Sweetness compared to sugar and is 3 times of Acceptable Daily Intake ADI.[16] while participants of group A were given 10 gm of cellulose, using a physical balance electrically operated with 0.001mg precision. The arterial pulse, systolic and diastolic blood pressure were also measured at 30, 60, 90 and 120 minutes.

The blood sugar levels were checked at 0 and then at 120 minutes in all the participants.

Data Analysis

Data was analyzed by SPSS version 16. The quantitative data was presented as mean and standard deviation. Difference between two groups was calculated using student t test. The 95% confidence interval was taken and p-value less than 0.05 was considered significant. One way ANOVA was used to show the difference within the groups and between the groups.

RESULTS

Table 1: acute effect of non-nutritive sweeteners on blood glucose levels, and pulse at different time intervals.

Variables	Group A (Control)	Group B (Sucralose)	Group C (Aspartame)	Group D (Acesulfame)	P value A+B	P value A+C	P value A+D	P value B+C	P value B+D	P value C+D
Age	18.82±0.80	18.60±0.57	18.64±0.59	18.64±0.59	0.117	0.206	0.206	0.733	0.733	1.00
Glucose-0	132.98±5.95	132.88±5.86	132.52±5.75	132.76±5.78	0.933	0.695	0.852	0.757	0.918	0.836
Glucose 120 Min	134.82±7.24	134.4±5.86	134.96±7.33	135.42±6.83	0.775	0.924	0.671	0.705	0.476	0.746
Pulse 0	78.68±8.02	77.18±6.70	77.38±10.48	77.38±9.34	0.313	0.488	0.450	0.910	0.912	0.992
Pulse 30 min	79.44±6.85	77.98±17.38	83.32±9.98	83.38±8.98	0.582	0.026	0.015	0.063	0.054	0.975
Pulse 60 min	78.22±8.42	75.96±15.70	83.26±10.18	83.0±8.73	0.372	0.008	0.006	0.007	0.007	0.891
Pulse 90 min	78.40±12.14	75.78±15.82	82.28±9.89	83.96±8.83	0.355	0.083	0.010	0.016	0.002	0.373
Pulse 120 min	79.32±7.30	77.72±6.07	84.16±10.73	83.22±9.90	0.237	0.010	0.027	0.000	0.001	0.650

Table 2: Acute effect of non-nutritive sweetener at systolic and diastolic blood pressure at different time intervals.

Variables	Group A Control	Group B Sucralose	Group C Aspartame	Group D Acesulfame	P value A+B	P value A+C	P value A+D	P value B+C	P value B+D	P value C+D
Systolic Pr-0 min	115.12±9.09	113.82±9.61	112.12±9.6	113.18±9.35	0.489	0.112	0.296	0.379	0.737	0.578
Systolic Pr-30 min	115.64±8.00	114.40±9.94	113.40±10.17	113.0±1.15	0.494	0.224	0.152	0.620	0.488	0.844
Systolic Pr-60 min	116.92±8.98	112.60±11.21	109.82±11.39	110.60±11.0	0.166	0.001	0.002	0.223	0.078	0.715
Systolic Pr-90 min	117.84±10.2	114.20±11.65	112.54±11.18	113.50±12.36	0.100	0.015	0.059	0.469	0.771	0.685
Systolic Pr-120 min	117.16±8.62	113.98±11.14	112.02±10.54	113.36±10.44	0.114	0.009	0.050	0.369	0.775	0.525
Diastolic Pr-0	75.56±6.17	75.20±7.47	73.70±7.27	74.60±6.91	0.793	0.171	0.466	0.312	0.678	0.527
Diastolic Pr-30 min	76.74±5.97	76.92±7.17	78.98±8,30	75.76±10.45	0.892	0.125	0.566	0.188	0.519	0.091
Diastolic Pr-60 min	76.64±6.37	75.32±6.65	74.96±5.93	76.00±5.19	0.314	0.176	0.583	0.776	0.570	0.354
Diastolic Pr-90 min	76.80±6.04	75.58±6.75	74.74±6.44	75.92±6.00	0.344	0.103	0.467	0.526	0.791	0.346
Diastolic Pr-120 min	77.00±5.77	76.32±6.49	76.12±7.98	77.90±8.99	0.581	0.424	0.553	0.353	0.316	0.918

Table 3: One way ANOVA between and within the groups.

Variables	Mean Square Between group	Mean Square Within group	F value	p value
Glucose 0	1.965	34.122	0.058	0.982
Glucose 120 min	10.200	52.695	0.194	0.901
Pulse – 0 min	23.980	70.651	0.313	0.816
Pulse 30min	376.620	132.479	2.843	0.039
Pulse 60 min	651.153	124.429	5.233	0.002
Pulse 90 min	478.173	146.171	3.271	0.022
Pulse 120 min	474.178	75.909	6.247	0.000
Systolic pressure 0	76.653	88.762	0.886	0.449

Systolic pressure 30 min	69.353	92.396	0.751	0.523
Systolic pressure 60 min	503.138	114.738	4.385	0.005
Systolic pressure 90 min	268.093	129.672	2.067	0.043
Systolic pressure 120 min	237.473	104.726	2.268	0.040
Diastolic pressure 0	33.045	48.647	0.679	0.566
Diastolic pressure-30 min	156.978	47.966	3.273	0.122
Diastolic pressure-60 min	27.700	36.798	0.753	0.522
Diastolic pressure -90 min	36.333	39.946	0.910	0.437
Diastolic pressure-120 min	66.013	42.397	1.533	0.207

RESULTS

Table 1 shows acute effect of non-nutritive sweeteners on blood glucose levels and pulse at different time intervals. The study groups showed a mean age of 18.64±0.66 years. A non-significant difference was noticed regarding random blood glucose levels before (p – 0.933, 0.695, 0.852) and 120 minutes after (p - 0.775, 0.924, 0.671) ingestion of sucral (group B), aspartame (group C) and acesulfame potassium (group D) compared to control group respectively. A same trend of non-significant difference was noticed when random blood glucose levels at 0 and 120 minutes in participants of group B were compared with that of group C (p-0.757, 0.705) and group D (p-0.918, 0.476) respectively. Similarly the difference for random blood glucose between group C and D was also non-significant at 0 and 120 minutes (p-0.836, 0.746) respectively. The pulse rate at 0 time between group A and B (p-0.313), group A and C (p-0.488), group A and D (p-0.450) were non-significant. When the heart rate at 30, 60, 90 and 120 minutes between control (group A) and the participants of group B, (0.582, 0.372, 0.355, 0.237 respectively, was compared, it was found to be non-significant. However, a statistically significant difference ($p<0.05$) was noticed when heart rate at 30, 60, 90,and 120 minutes between participants of group A was compared with that of group C and group D. A non-significant difference was seen when pulse rate at 0 and 30 minutes of group B was compared with that of group C (0.910, 0.063) and group D (p-0.912, 0.054) respectively, a same trend of non-significant (p-0.992, 0.975) at 0,and 30 minutes pulse rate was present between participants of group C and D. When pulse rate at 60 90, and 120 minutes in participants of group B was compared with that of group C and D, a significant difference was found ($p<0.05$), however, the difference was non-significant ($p>0.05$) between participants of groups C and D at 30, 60,90 and 120 minutes.

Table 2 shows acute effect of non-nutritive sweetener at systolic and diastolic blood pressure Systolic pressure at 0 and 30 minutes showed a non-significant difference between participants of group A and that of B (0.489, 0.494), group C (0.112, 0.224) and D (0.296,

0.152) respectively. A same trend of non-significant difference was noticed when systolic pressure at 60, 90 and 120 minutes of group A was compared with that of group B (0.166, 0.100, 0.114) respectively, however, the difference regarding systolic pressure at 60, 90 and 120 minutes was statistically significant ($p<0.05$) when participants of group A were compared with that of group C and D. The difference for systolic blood pressure was non-significant at 30, 60, 90 and 120 minutes between participants of group B and C (0.620, 0.223, 0.469, 0.369) respectively and between group B and group D (0.488, 0.078, 0.771, 0.775) respectively. A similar trend of non-significance for systolic pressure was noticed between group C and D at 30, 60, 90 and 120 minutes (0.844, 0.715, 0.685, 0.525) respectively.

The diastolic pressure at 0, 30, 60, 90 and 120 minutes between the control and the study groups B, C and D was found to be non-significant ($p>0.05$). A same trend of non-significant difference ($p>0.05$) was noticed when diastolic pressure between the participants of group B were compared with that of group C and D. Similarly the diastolic pressure between groups C and D showed a non-significant difference at different time intervals (o, 30, 60, 90 and 120 minutes).

The systolic pressure at 60, 90 and 120 minutes showed significant difference ($p<0.05$) within and between the groups, however non-significant difference was seen at 0 and 30 minutes (0.449, 0.523) times respectively.

The diastolic pressure at different time intervals (0, 30, 60, 90 and 120 minutes) between and within the groups were found to be non-significant ($p>0.05$).

Table 3 shows one way analysis of variance between and within the groups.

The glucose levels were non-significant within and between the groups at 0 and 120 minutes (0.982, 0.901) respectively. The statistically significant difference ($p<0.05$) was noticed when pulse rate at 30, 60, 90 and 120 minutes were compared within the group and between the groups, however, the difference for pulse rate at 0 time was non-significant (p-0.816) between and within the groups.

The ANOVA showed significant difference ($p<0.05$) between and within the groups regarding systolic pressure at 60, 90 and 120 minutes, however, it was non-significant at 0

and 30 minutes (p-0.499, 0.523) respectively. The diastolic pressure at 0, 30, 60, 90 and 120 minutes within and between the groups was non-significant (p>0.05).

DISCUSSION

Our results showed no effects on random blood glucose levels after taking the NNS (sucralose, aspartame and Acesulfame potassium) in study groups compared to control group. These results are consistence with Brown et al[17] who showed no significant effect on blood glucose levels after oral consumption of NNSs without co-administration of glucose. The Jing Ma et al[18] showed that when Sucralose was administered by intraduodenal infusion in combination with glucose, there was no marked effect on blood glucose however,[19] GLP-1 was elevated in healthy as well as in patients with type 1 diabetes. In vivo, the expression of sodium glucose transporter-1, Na^+-glucose cotransporter and glucose absorption increases after oral ingestion of sucralose.[20]

Our results showed significant raised levels of pulse and blood pressure in participants who were given aspartame and acesulfame compared to control. These results are consistent with Kiritsy et al[21] showed acute effects of aspartame on systolic blood pressure in spontaneously hypertensive rats. Dagfinn et al[22] indicated that daily consumption of artificially-sweetened beverages showed significantly increased risk of hypertension and vascular events, equal in magnitude to daily consumption of sugar-sweetened beverages.

Aspartame, comprising half of the phenylalanine molecules, elevates blood and brain tyrosine levels which being hydrolyzed to phenylalanine. The phenylalanine in turn converts to catecholamine-dopamine, epinephrine and norepinephrine. The phenylalanine and catecholamine might cause nerve damage in the brain, which in turn affects signaling transmissions from brain to heart, causing arrhythmia or an irregular heart-beat, palpitations, dizziness, fainting, weakness and shortness of breath. The conversion also results raised blood pressure. Aspartame also has evidenced peripheral vasomotor features like Raynaud phenomenon and the pulmonary hypertension.[23] The likelihood of pulmonary hypertension induced by the vasoconstrictive effects of aspartame products.[22] Even sudden death among previously well individuals including pilots, drivers and athletes is also reported to aspartame and its breakdown products.[24]

CONCLUSION

The effects of the NNSs on glucose metabolism are not clear, however, there is strong clinical association between artificial sweeteners and cardiometabolic outcomes. There is a need for further research to address the evidence gaps related to health effects of NNSs use.

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