The Effect of Soy Milk as an Adjunct in Reducing Blood Pressure Among Adult Hypertensive FM-OPD Patients at Quezon City General Hospital

Donato Zabat Lazaro, MD

Background: Hypertension is the most common condition seen in primary care. Despite various researches and evolving medical arts, it is still considered as the biggest single risk factor for deaths worldwide.
Objective: To determine whether non-pharmacologic management such as intake of soy milk will be effective as an adjunct in reducing elevated blood pressure among adult patients at the Quezon City General Hospital – Out Patient Department.
Methodology: Forty hypertensive patients consulting at the Family Medicine – Out Patient Department for elevated blood pressure satisfying the inclusion criteria were enrolled in the study.
Design: Open-label, randomized controlled crossover trial
Data Collection: The subjects were grouped to non-soy milk and soy milk. Parameters such as blood pressure, heart rate and respiratory rate were recorded daily then summarized after second and fourth week. A wash out period for 1 week was observed for the soy milk group then a crossover of the arm was done for four weeks.
Results: There were no significant differences in reducing Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) observed both at Phase I and Phase II in non-soy milk and soy milk group. Significant reduction in the Systolic Blood Pressure (SBP) and Heart Rate (HR) were observed at Phase II of soy milk group with p-value of 0.018 at week 2 and 0.002 at week 4 respectively.
Conclusion: This study has shown that patients may benefit from using soymilk as an adjunct to hypertensive medication in lowering blood pressure and heart rate

Keywords: Hypertension, soy milk, Losartan

Introduction

Hypertension is still the most common condition seen in primary care setting despite the various researches and regimens in treating high blood pressure. It is considered as the biggest single risk factor for deaths worldwide that leads to myocardial infarction, stroke and renal failure.[1] According to the World Health Organization (WHO) in 2016, hypertension causes 7 million deaths every year while 1.5 billion people suffer due to its complications[1] and in 2012, 21 percent of Filipino adults are hypertensive according to the Philippine Society of Hypertension (PSH).[2] Considerable attention therefore should be paid to the prevention and control of hypertension

Like in any diseases, pharmacologic and non-pharmacologic management are equally important, however, with the mainstay of hypertensive therapy being pharmacotherapy, interventions such as lifestyle and dietary modification often are overlooked. The Eight Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

* From the Department of Family and Community Medicine, Quezon City General Hospital and Medical Center

recommends lifestyle and dietary modification for all patients with hypertension and prehypertension.[3]

The prevalence of complementary medicine use in the Philippines is 78 percent.[4] Soymilk has been consumed for centuries in Asian countries. Many potential benefits have been linked to intake of soy products according to epidemiological investigations.[5] It has received an increasing scientific interest for its beneficial effects on cardiovascular health such as lowering incidences of coronary heart diseases, atherosclerosis, type 2 diabetes, and decreased risk of certain types of carcinogenesis (breast and prostate cancers) as well as better bone health and relief of menopausal symptoms.[6]

Studies have been made on the effectiveness of diet modification in reducing Blood Pressure (BP), though limited, one of which is the inclusion of Soy based products in the diet.[6] Nevala, et al.[7] found that a soy-based diet attenuated the development of hypertension in spontaneously hypertensive rats. Clinical trials were also conducted among humans where soymilk was given in hypertensive patient without hypertensive drugs. Washburn, et al.[8] found that soy protein supplementation significantly reduced diastolic blood pressure (−5 mm Hg) in perimenopausal women, while another study was done by Wang, et al.[14] that focused more on the pharmacokinetic effect of Soymilk to Losartan rather than on the direct effect in reducing high blood pressure. To date, there is no local study on the use of soymilk in lowering blood pressure. Therefore, this study focuses on assessing the effect of soy milk as an adjunct to a hypertensive medication in reducing blood pressure

The objective of the study was to determine whether non-pharmacologic management such as intake of soy milk will be effective as an adjunct in reducing elevated blood pressure (BP of 140-159/ 90-99) among adult patients, 19-60 years old, at the FM-OPD of QCGH.

This open-label, randomized controlled crossover trial involved patients 19 years to 60 years old who consulted at Quezon City General Hospital- Department of Family and Community Medicine Out Patient Clinic from June 15 to July 31, 2018. They are newly-diagnosed hypertensive patients and who signed the informed consent for the study.

Inclusion Criteria

1. Must be 19 to 60 years old
2. Must be a newly-diagnosed hypertensive patient
3. Must have a baseline Systolic Blood Pressure (SBP) of 140mmHg to 159 mmHg and/or a baseline Diastolic Blood Pressure (DBP) of 90mmHg to 99 mmHg

Exclusion Criteria

1. Patients with diabetes, cardiac disease, stroke, renal disease, arthritic disease, lung disease, and with pain upon consult
2. Presence of neurologic deficits/symptoms upon consult
3. Hypersensitivity to soy products

Ethical Aspects

Subjects were informed about the objectives, methods, potential benefits and/or disadvantages of the trial. Written informed consent was obtained before inclusion in the study. Subjects were free to decide about their inclusion in the study or to stop at any time.

Methods

Forty (40) hypertensive patients consulted at the FM-OPD for elevated blood pressure and satisfying the inclusion criteria, and none of the exclusion criteria, were enrolled in the study. The demographic profile was obtained through patient interview. These include name, age, sex, civil status, educational attainment, occupation, and presence of co-morbidities.

Prior to the start of the study, all subjects were advised to have a 2 week soy-free diet. For the 1st week upon enrolment, Losartan 50 mg/tab once a day was introduced as maintenance medication for all subjects. Parameters such as daily BP, heart rate and respiratory rate monitoring were done then averaged and recorded on the 7th day. After a week, subjects were randomized to either the soymilk or the non-soymilk group. The soymilk group took Losartan plus 1000 ml serving (8 grams of soy protein) of unsweetened commercial brand of soy milk for three times a week (Monday- Wednesday – Friday) and the Non Soymilk group took Losartan alone; both for the duration of 4 weeks. Parameters were taken daily, summarized and recorded at the end of week 2 and week 4. After 4 weeks, a 1-week soymilk – free washout period was implemented, and then a crossover was done for the next 4 weeks.

Participants were instructed to have blood pressure monitoring at their home, at nearby clinics or hospital, twice a day, at 7am and 7pm, based on the recommended guidelines of JNC 8. Blood pressure was measured after the patients have emptied their bladder and seated for five minutes with back supported and legs resting on the ground (not crossed). Arm

used for measurement should rest on a table, at heart-level. A sphygmomanometer with stethoscope or automated electronic device with the correct arm cuff size was used. Two readings one to two minutes apart were taken, and readings were averaged. Blood pressure was measured in both arms at initial evaluation. The higher readings were used for measurements and recorded on BP monitoring sheet that were provided to them. Follow-ups were every Wednesday and Friday. The investigator got the BP readings of participants in every follow-up using a sphygmomanometer and results were recorded and summarized on the 2nd and 4th week. The mean changes in Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were the main outcomes measured in this study. The average pre- and post-intervention SBP and DBP measurements were recorded and the Mean Arterial Pressure (MAP) was computed accordingly. The difference or change in values pre- and post- intervention was obtained.

For the Diet protocol, in the selection of unsweetened soy milk for the study, protein contents were measured in commercially-available preparations. Subjects were referred to the Hospital Nutritionist for hypertensive diet, DASH diet as recommended by AHA, with and without soy milk, prior to the study and were advised to follow it responsibly. Participants were instructed to record intakes in their daily intake diaries.

For standardization of Physical activity (PA), the American Heart Association Recommended Guidelines for Physical Activity for Hypertensive Patients were used. Participants were advised to get the equivalent of at least 150 minutes (two hours and 30 minutes) per week of moderate-intensity physical activity, such as brisk walking. Their activities were recorded in their PA diaries.

Prior to the start of data collection for this study, the Family Medicine (FM) residents on Duty (ROD) at the Out-Patient Department (OPD) of Quezon City General Hospital (QCGH) were oriented regarding the recruitment of participants, prescribing the interventions and proper collection of data. The residents on duty were oriented and instructed initially as a group, then individually. They were provided with copies of the Inclusion/Exclusion Criteria, General Instructions, Standardized Script in Asking for Consent, Intervention Instructions and Pre-Randomized Treatment Group Assignment List. Patients were randomly assigned to the experimental groups. A thorough history and physical examination were obtained by the ROD to determine whether the participant can be included in the study. The patient who satisfied the inclusion criteria and none of the exclusion criteria was considered as a participant of the study. Upon consent, Baseline SBP, DBP, HR, RR and MAP were all taken. Data were recorded and submitted by the ROD to the investigator.

Results and Discussion

This study identified significant reductions in the Systolic Blood Pressure (SBP), Diastolic Blood Pressure and Mean Arterial pressure (MAP) during soya milk interventions, especially during the second period when it is combined with the hypertensive medication (Losartan). Soya protein consumption significantly reduced SBP and DBP, this is in accordance with the study done by Dong, et. al in year 2011.[12]

Soy milk is a plant-based drink produced by soaking and grinding soybeans, boiling the mixture, and filtering out remaining particulates. Nutrients called isoflavones - may help to lower blood pressure. Isoflavones boost production of enzymes that make nitric oxide, which helps relax blood vessels and lower blood pressure.[12]

Losartan is the anti-hypertensive medication used in this study. It is a selective, competitive angiotensin II receptor type 1 antagonist, reducing the end organ responses to angiotensin II and metabolized by CYP2C9 and CYP3A4 to an active metabolite, E-3174, which has greater antihypertensive activity than the parent compound.[13] In a previous study, Soy extract has been shown to be an activator of CYP2C9 and CYP3A4 in vitro.[14] This probably explains the data of this study wherein co-administration of Soy Milk with Losartan resulted in an added decrease in blood pressure of the study participants.

In the present study, 40 hypertensive patients participated with Mean age of 38 years old +/- 4 years. Majority (70%) were male while 30% were female. Most of them (65%) were married while 35% were single. Most (78%) attained college education, 13% attained vocational while 10% pursued post-graduate education. 78% were employed, 18% were self-employed while the remaining 5% were unemployed. (Table 1)

The participants were divided into 2 study groups: Group A and Group B. By statistics, there was no significant difference between the two groups in terms of baseline demographics.

Physical Activities

Physical exercise has positive effects on blood pressure whether or not a person has hypertension, producing average reductions of 4 mm Hg in systolic blood pressure and 3 mm Hg in diastolic blood pressure.[10] It is recommended that patients with prehypertension or hypertension exercise for 30 minutes on most days of the week. [11]

In this study, 95-100% of the participants reported that they got an equivalent of at least 150 minutes per week of moderate-intensity physical activity within the study period of 12 weeks. No significant difference was found between the groups in terms of physical activities. This standardized the effect of exercise in both groups.

Progress of patients through trial.

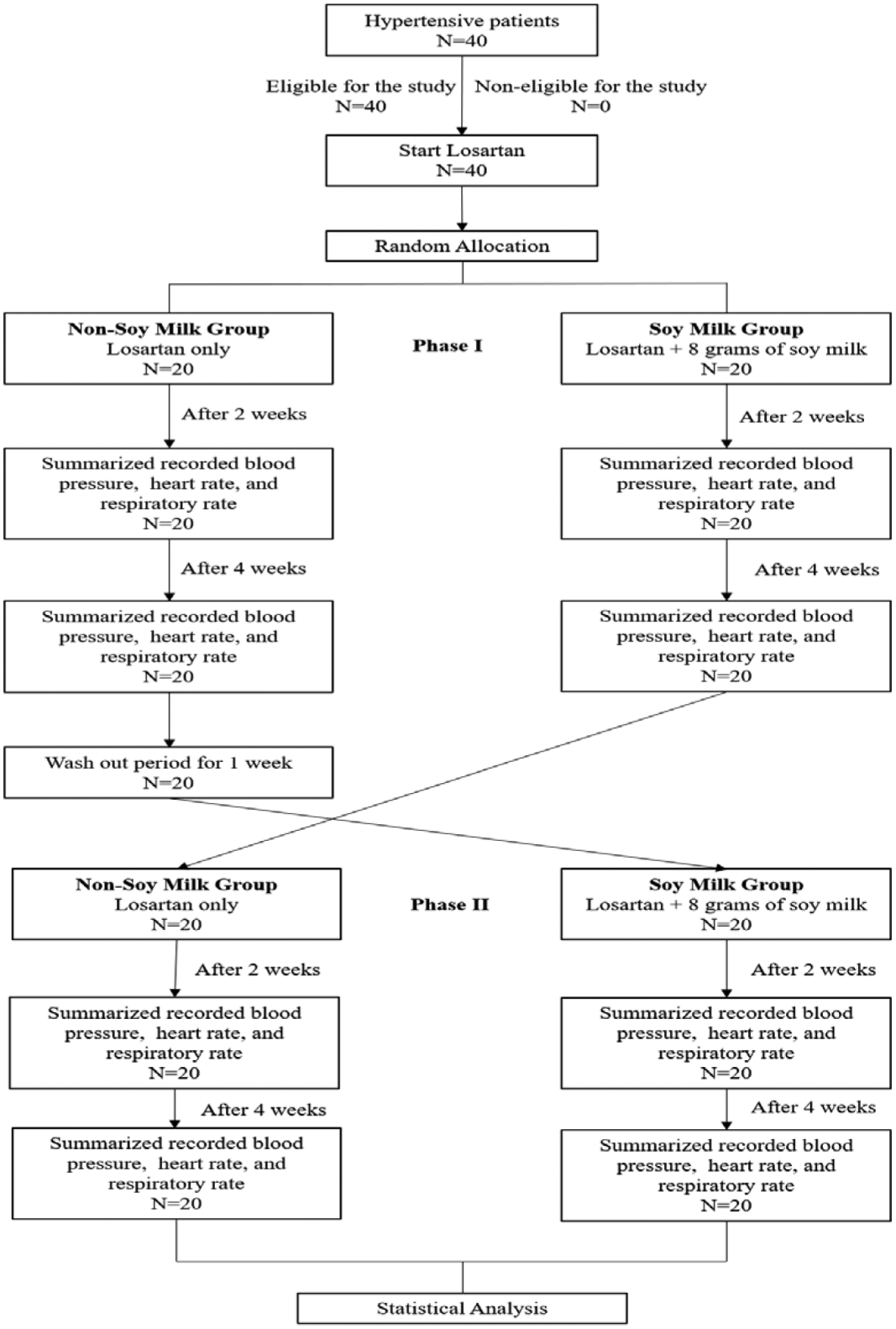


Table 1. Demographic profile (N = 40)

	Total Sample		Group A		Group B		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age	38	4	38	5	38	3	1.000
	#	%	#	%	#	%	
Sex							
Male	28	70	14	70	14	70	1 .000
Female	12	30	6	30	6	30	
Civil Status							
Single	14	35	7	35	7	35	1.000
Married	26	65	13	65	13	65	
Educational Attainment							
College	31	77.5	15	75	16	80	0.890
Vocational	5	12.5	3	15	2	10	
Post-grad	4	10	2	10	2	10	
Occupation							
Employed	31	77.5	15	75	16	80	0.19
Self-employed	7	17.5	5	25	2	10	
Unemployed	2	5	0	0	2	10	
Comorbidities							
None	40	100	20	100	20	100	1.000
Consent							
Yes	40	100	20	100	20	100	1.000

Table 2. Physical activity.

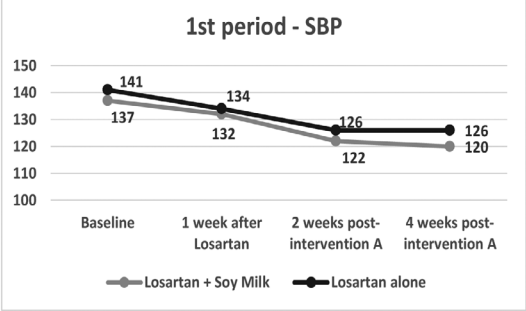
		Group A		Group B		p-value
		#	%	#	%	
Week 1	Yes	20	100	20	100	-
	No	0	0	0	0	
Week 2	Yes	19	95	17	85	0.292
	No	1	5	3	15	
Week 3	Yes	19	95	19	95	1
	No	1	5	1	5	
Week 4	Yes	19	95	19	95	1
	No	1	5	1	5	
Week 5	Yes	20	100	20	100	-
	No	0	0	0	0	
Week 6	Yes	19	95	19	95	1
	No	1	5	1	5	
Week 7	Yes	20	100	19	95	0.311
	No	0	0	1	5	
Week 8	Yes	19	95	18	90	0.548
	No	1	5	2	10	

Systolic Blood Pressure (SBP)

At baseline, mean SBP for the two groups were 137 and 141. One week after taking Losartan, mean SBP of both groups dropped to 132 and 134. In the first period, two (2) weeks post-intervention, SBP of Losartan + Soy Milk group decreased by an average of 10 points from 132 to 122; while SBP of Losartan alone group decreased by an average of only 9 points from 134 to 126.

By four (4) weeks post-intervention, SBP of Losartan + Soy Milk group decreased by an average of 12 points from 132 to 120; while SBP of Losartan alone group remained 126, the same as in 2 weeks post-intervention.

In the first period, there was not enough evidence to show a significant difference between the two groups in terms of mean change in SBP after 2 weeks and 4 weeks of intervention.



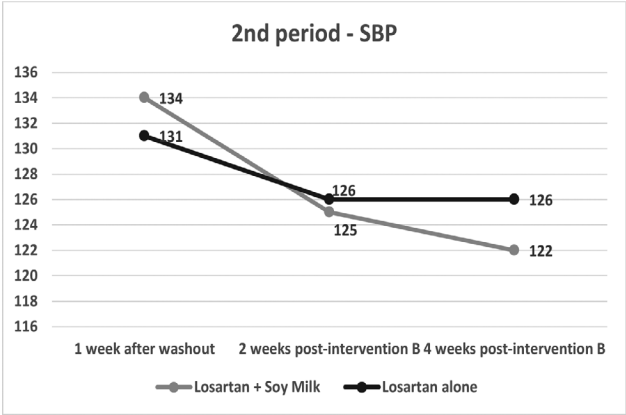
1st period Change in SBP	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-10	5	-9	5	0.531
After 4 weeks	-12	6	-9	5	0.054

Figure 1. Decrease in systolic blood pressure between the two groups before the crossover.

One (1) week after washout, mean SBP for the two groups went back up to 134 and 131. In the second period, two (2) weeks post-intervention, SBP of the Losartan + Soy Milk group declined by an average of 9 points from 134 to 125; while SBP of the Losartan alone group decreased by an average of only 5 points from 131 to 126.

By four (4) weeks post-intervention, SBP of the Losartan + Soy Milk group already dropped by an average of 12 points from 134 to 122; while SBP of the Losartan alone group stayed at 126, same as in 2 weeks post-intervention.

In the second period, independent samples t-test showed a significant difference in the change between the two intervention groups, in terms of mean change in SBP. This shows the decrease in SBP effect of intervention with Soy milk after 4 weeks.



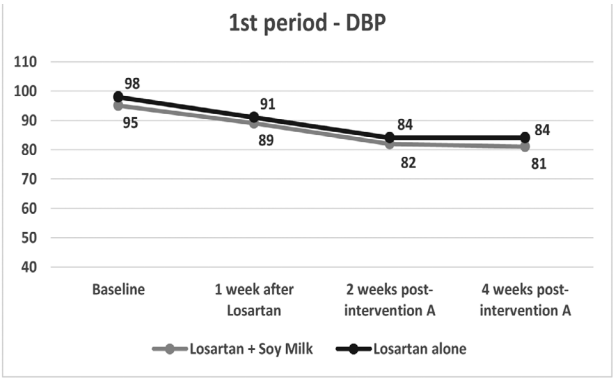
2nd period Change in SBP	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-9	5	-5	5	0.018
After 4 weeks	-13	6	-5	5	0.000

Diastolic Blood Pressure (DBP)

At baseline, mean DBP of both groups were 95 and 98. Mean DBP dropped to 89 and 91, respectively, after 1 week use of Losartan group. Two (2) weeks post-intervention, DBP of Losartan + Soy Milk group declined by an average of 7 points from 89 down to 82; while DBP of the Losartan alone group decreased by an average of 7 points from 91 down to 84.

By four (4) weeks post-intervention, DBP of the Losartan + Soy Milk group decreased by an average of 8 points from 89 down to 81; while DBP of the Losartan group remained at 84, same as in 2 weeks post-intervention.

In the first period, there was not enough evidence to show a significant difference between the two groups in terms of mean change in DBP after 2 weeks and 4 weeks of intervention.



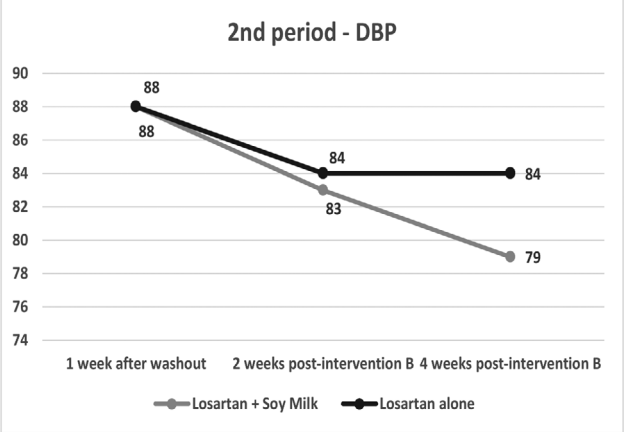
1st period Change in DBP	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-7	6	-7	6	0.582
After 4 weeks	-8	6	-7	6	0.788

One (1) week after washout, mean DBP of the two groups went back up to an average of 88.

Two (2) weeks post-intervention, in the second period, DBP of the Losartan + Soy Milk group declined by an average of 5 points from 88 down to 83; while DBP of the Losartan alone group declined by an average of only 4 points from 88 down to 84.

Four (4) week post-intervention, DBP of the Losartan + Soy Milk group dropped by an average of 9 points from 88 down to 79; while DBP of the Losartan alone group stayed at 84, same as in 2 weeks post-intervention.

In the second period, there was not enough evidence to show a significant difference between the two groups, in terms of mean change in DBP 2 weeks post-intervention. On the other hand, independent samples t-test showed a significant difference between the two groups, in terms of mean change in DBP 4 weeks post-intervention.



2nd period Change in DBP	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-5	5	-4	5	0.539
After 4 weeks	-9	4	-4	5	0.001

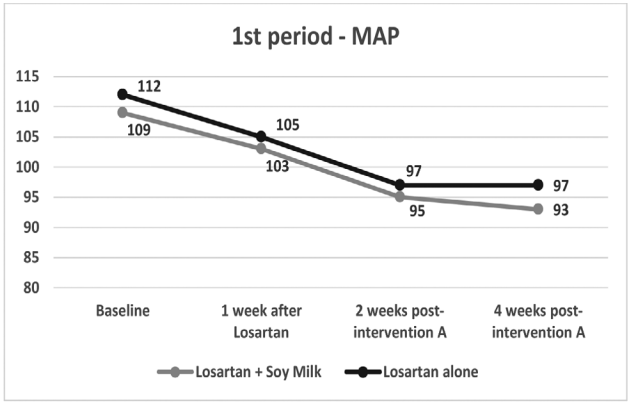
Mean Arterial Pressure (MAP)

At baseline, mean MAP of the two groups were 109 and 112. Mean MAP dropped down to 103 and 105, respectively, 1 week after Losartan use.

Two (2) weeks post-intervention, MAP of the Losartan + Soy Milk group went down by an average of 8 points from 103 down to 95; while MAP of the Losartan alone group also went down by an average of 8 points from 105 down to 97.

After 4 weeks post-intervention, MAP of the Losartan + Soy Milk group went down by an average of 10 points from 103 down to 93; while MAP in the Losartan only group remained at 97, same as in 2-weeks post-intervention.

In the first period, there was not enough to show a significant difference between the two groups, in terms of mean change in MAP.



1st period Change in MAP	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-8	4	-8	3	0.822
After 4 weeks	-10	4	-8	3	0.212

One (1) week after washout, MAP for both groups went up to 103 and 102.

Two (2) weeks post-intervention in the second period, MAP of the Losartan + Soy Milk group went down by an average of 7 points from 103 down to 96; while MAP of the Losartan only group went down by an average of 5 points from 102 down to 97.

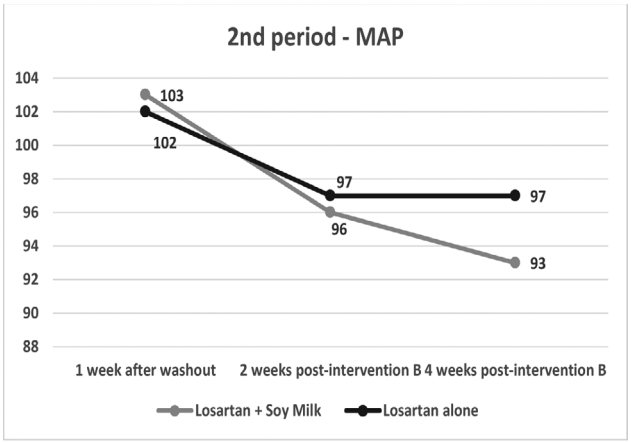
After 4 weeks post-intervention, MAP of the Losartan + Soy Milk group went down by an average of 10 points from 103 down to 93; while MAP of the Losartan only group remained at 97, same as in 2-weeks post-intervention.

In the second period, there was not enough evidence to show a significant difference between the two groups, in terms of mean change in MAP two weeks post-intervention. However, independent samples t-test showed a significant difference between the mean change in MAP four-week post-intervention.

Heart Rate

At baseline, mean heart rate of both groups was 76. One (1) week after using Losartan, mean heart rate of both groups dropped to 73.

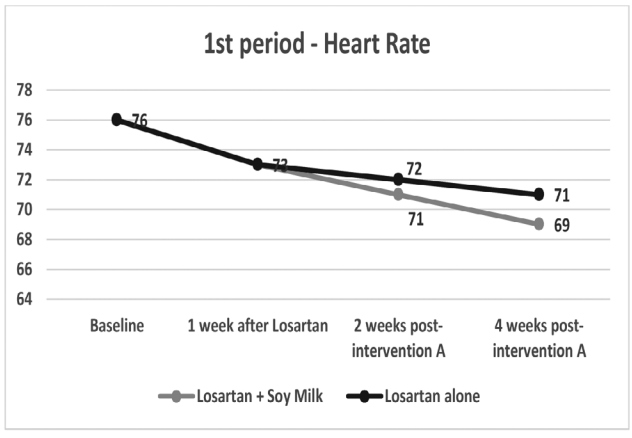
Two (2) weeks post-intervention, mean heart rate of Losartan + Soy Milk group declined by an average of 2 points from 73 down to 71; while mean heart rate of Losartan alone group decreased by an average of 1 point from 73 down to 72.



2nd period Change in MAP	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-7	4	-5	4	0.06
After 4 weeks	-10	3	-5	4	0.00

Four (4) weeks post-intervention, mean heart rate of Losartan + Soy Milk group declined by an average of 4 points from 73 down to 69; while mean heart rate of Losartan alone group decreased by an average of 2 point from 73 down to 71.

There was not enough evidence to show any significant difference between the two groups in terms of mean change in heart rate in the first period.



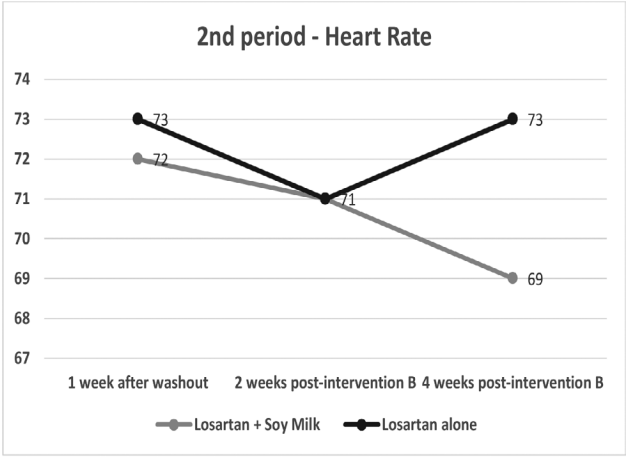
1st period Change in HR	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-2	2	-1	2	0.862
After 4 weeks	-4	2	-2	3	0.096

One (1) after washout, mean heart rate of both groups went up to 72 and 73.

Two (2) weeks post-intervention in the second period, mean heart rate of the Losartan + Soy Milk group went down by an average of 1 point from 72 down to 71; while mean heart rate of Losartan alone group went down by an average of 2 points from 73 down to 71.

By four (4) weeks post intervention, mean heart rate of the Losartan + Soy Milk group went down by an average of 3 points from 72 down to 69, while mean heart rate of the Losartan alone group reverted back to 73.

In the second period, there was not enough evidence to show a significant difference between the two groups, in terms of mean change in heart rate 2 weeks post-intervention, but independent samples t-test showed a significant difference in the mean change in heart rate of the two groups 4 weeks post intervention.



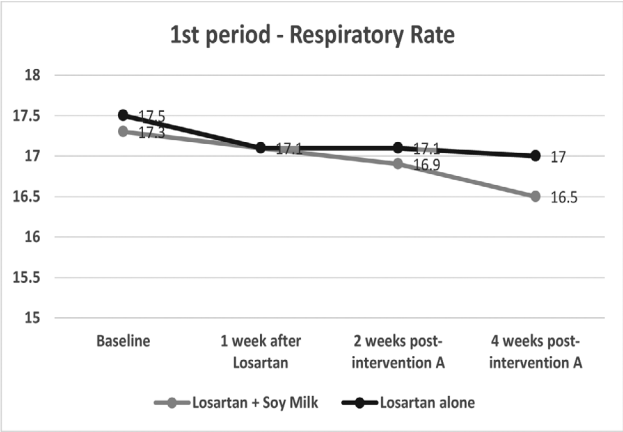
2nd period Change in HR	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-1	3	-2	3	0.643
After 4 weeks	-3	4	0	4	0.002

Respiratory Rate

At baseline, mean respiratory rate (RR) of both groups were 17.3 and 17.5. After 1 week of Losartan use, mean RR of both groups went down to 17.1. Two (2) weeks post-intervention, respiratory rate in the Losartan + Soy Milk group went down by an average of 0.2 point from 17.1 down to 16.9; while respiratory rate in the Losartan alone group remained stable at 17.1.

Four (4) post-intervention, RR in the Losartan + Soy Milk group went down by average of 0.6 point from 17.1 down to 16.5; while RR in the Losartan alone group went down by an average of 0.1 point from 17.1 down to 17.

There was not enough evidence to show a significant difference between the two groups in terms of mean change in RR 2 weeks post-intervention. However, t-test showed a significant difference between the two groups in terms of mean change in RR after 4 weeks post-intervention.



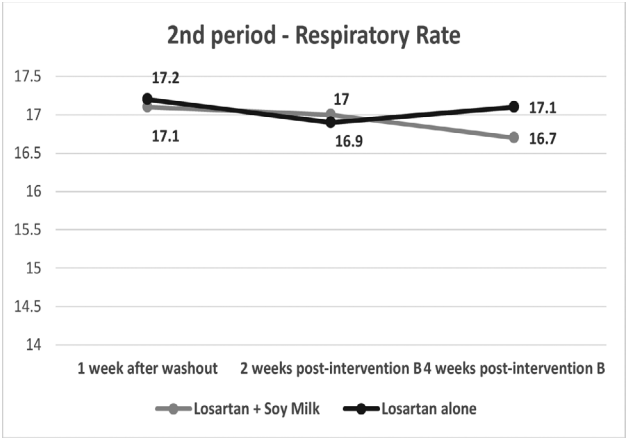
1st period Change in RR	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-0.2	1	0.0	1	0.353
After 4 weeks	-0.6	1	-0.1	1	0.01

One week after washout, mean RR of both groups went back up to 17.1 and 17.2, Two (2) weeks post-intervention, RR of Losartan + Soy Milk group went down by an average of 0.1 point from 17.1 down to 17; while RR of Losartan alone group went down by 0.3 point from 17.2 down to 16.9.

Four (4) weeks post intervention, RR of Losartan + Soy Milk group went down by an average of 0.4 point from 17.1 down to 16.7; while RR of Losartan alone group went down by an average of 0.1 point from 17.2 down to 17.1.

There was not enough evidence to show a significant difference between the two groups, in terms of mean change in RR in the second period.

Filipinos are fond of Soy products, from the popular snack "Taho" to Soy sauce.[14] The findings of this study have potential public health implications here in the Philippines. Although the BP reductions reported are moderate , a reduction of 5-6mmHg in SBP and 4-5mmHg in DBP, would be expected to substantially reduce the risk of stroke and CHD.[14] Given the high prevalence of hypertension[15], even a slight reduction in BP may contribute to a considerable public health benefit from soya protein consumption. Moreover, when used for other purposes, such as improving lipid profiles[16] the moderate hypotensive effects of soya protein doubtlessly provide extra benefits.



2nd period Change in RR	Losartan + Soy Milk		Losartan alone		p-value
	Mean	SD	Mean	SD	
After 2 weeks	-0.1	1	-0.3	1	0.411
After 4 weeks	-0.4	1	-0.1	1	0.183

Short duration of intervention, unmeasured dietary factors that potentially influenced BP outcomes, such as dietary Na and K intake during the intervention, standardization of BP apparatus used, were the limitations in this study that must be considered while interpreting the results.

Conclusion and Recommendation

As the intervention was implemented for both sexes and ages 19 to 60 years old, Hypertensive patients, results indicate that patients may benefit from using soy milk as an adjunct to hypertensive medications, especially to Losartan, for decreasing blood pressure and cardiac rate.

For other hypertensive medications, more studies are needed for confirming the effect of soy milk in BP reduction as an adjunct. More studies are needed to clearly understand the underlying mechanisms of BP influence by soy milk.

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