Original Article

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Effects of Flaxseed on Blood Pressure in Patients Taking Antihypertensive Drugs: A Randomized Trial

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Abstract

Background: The cardiovascular protective effects of consuming flaxseed, such as improving lipid profile and reducing inflammatory markers, have been studied in both animals and humans. This study aimed to assess the effects of flaxseed in patients taking antihypertensives and compare their blood pressure before and after daily consumption of flaxseed on days 0, 45, and 90.

Methods: This randomized trial was registered at ClinicalTrials.gov (Identifier: NCT0475950). A single-blind, parallel-group, prospective interventional randomized clinical trial was conducted using a lottery sampling method. Systemic blood pressure measurements were taken on days 0, 45, and 90. Descriptive statistics, including percentages, means, and standard deviations (SD), were calculated and presented. Inferential analyses involved independent t-tests and paired t-tests.

Results: Out of 72 hypertensive patients, 34% were males and 38% were females. There were no withdrawals from the study post-enrollment. The mean age of enrolled patients was 55.38 years, and the mean BMI was 26.53 kg/m^2. After 90 days, the flaxseed group demonstrated a significant reduction in mean Systolic Blood Pressure (SBP) from 151.62 to 131.89 mmHg, equating to a 13.01% decrease versus 4.77 % reduction in placebo group (p-value = 0.001). While there was also a reduction in mean Diastolic Blood Pressure (DBP) from 94.86 to 81.08 mmHg, corresponding to a 14.53% decrease in flaxseed group versus 5.7% reduction in placebo group, this change was not statistically significant (p-value = 0.082).

Conclusion: Flaxseed, when given alongside antihypertensives to patients with hypertension, can be effective and safe in maintaining blood pressure, thus reducing the risk of cardiovascular diseases.

Keywords: antihypertensives; flaxseed; clinical trial; cardiovascular diseases; blood pressure

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Background

Hypertension, a significant predisposing factor for fatality worldwide, is responsible for approximately 8.5 million cardiovascular deaths globally. Extensive research is underway to find cost-effective medications for managing hypertension.[1] The economic impact of treating hypertension is substantial, with an estimated direct and indirect cost of $51.2 billion in 2012-2013 and a projected total direct cost of $200 billion by 2030.[1]

Accurate diagnosis and evidence-based treatment of hypertension can effectively reduce cardiovascular events, disability, and death among patients.[2] The American Heart Association has updated its recommendations, defining hypertension as a blood pressure reading of 130/80 mm Hg or higher and providing new treatment guidelines that include lifestyle modifications and blood pressure-lowering drugs.[3] Hypertension is often referred to as the "silent killer" due to the absence of symptoms or warning signs, highlighting the importance of regular blood pressure monitoring.4 However, challenges persist in diagnosis and treatment due to reliance on cuff evaluations and the potential for long-standing, unpredictable, and side effect-linked treatment regimens.[4] Furthermore, only a fraction of patients who require blood pressure-lowering drugs have access to effective and affordable medications.[4]

Controlling elevated blood pressure, along with addressing other risk factors such as diabetes, dyslipidemia, and smoking, is crucial for preventing atherosclerotic diseases. Nutritional factors, accounting for approximately 40% of all cardiovascular diseases, including hypertension, have been studied in relation to the beneficial effects of flaxseed supplementation as a source of alpha-linolenic acid (ALA).[5-8]

The increasing prevalence of non-communicable diseases (NCDs) in Nepal, where NCDs account for nearly 50% of total deaths and cardiovascular disease represents 25% of these deaths, highlights the importance of addressing hypertension as a crucial risk factor.[9] Nepal has one of the highest proportions of hypertensive individuals, with an estimated prevalence of 27.3%.[9] Studies conducted in eastern Nepal have reported a hypertension prevalence of 33.9% among adults aged 20 years and above, emphasizing the need for interventions targeting cardiovascular risk factors.[10]

Flaxseed, derived from Linum usitatissimum L., is rich in alpha-linolenic acid, an omega-3 fatty acid. Its cardiovascular protective effects demonstrated through improvements in lipid profiles and reductions in inflammatory markers, have been investigated in both animal and human studies.[11-18] This study aims to further explore the potential use of flaxseed as a promising anti-hypertensive medication in our specific settings as no such flaxseed intervention in hypertensive patients were conducted yet in Nepal till date.

Methods

2.1. Study design

The present study was a single-blind, two parallel-group, prospective interventional randomized clinical trial conducted on hypertensive patients visiting the Medicine OPD [Out Patient Department) of B.P. Koirala Institute of Health Sciences, Dharan, Nepal.

2.1.1. Protocol registration

After receiving approval from the Institutional Review Committee, BPKIHS, and the Nepal Health Research Council, Kathmandu, the study was registered on clinicaltrials.gov with the registration number ID: NCT04759508.

2.1.2. Ethical statement

The study was approved by the Institutional Review Committee at BPKIHS, Dharan (Reference no: 347/077/078-IRC), and the Nepal Health Research Council, Kathmandu-Nepal (Reference no: 2608). Eligible participants received detailed information about the study, including potential adverse drug reactions, before providing informed consent and information on demographic factors and medical history.

2.2. Participant selection

2.2.1. Inclusion criteria

The inclusion criteria for participants were as follows:

- Patients aged 18 years and above with a confirmed diagnosis of hypertension
- Patients who agreed to take only physician-advised medicine.
- Patients who strictly followed the advised diet.
- Patients taking a single antihypertensive drug with equivalent doses.

2.2.2. Exclusion criteria

The following individuals were excluded:

- Patients suffering from serious or recurrent infections.
- Pregnant or breastfeeding women, immunodeficiency or HIV patients.
- Patients presenting with any mental abnormality that could impede or be influenced by the study procedure.
- Patients with a history of bleeding disorders.
- Hypersensitivity reaction or allergy to flaxseed.
- History of surgery within the past 6 weeks.
- Patients who did not give informed consent.
- Alcohol consumption > 30 U/day.
- Cigarette smoking > 2 packs/day.
- Patients taking multiple antihypertensive drugs.

2.3. Randomization and blinding

Randomization was conducted using the "lottery method," which is a common and basic randomization technique. Interventional and placebo groups were numbered on separate slips of paper of the same size, shape, and color. The slips were folded, mixed in a container, and a blindfolded selection was made. The required number of slips was selected for the desired sample size, and the respective groups were allocated in a sequence.

2.4. Sample size calculation

The number of participants required in each group was calculated using a power and sample size program. The sample size estimation for this study was based on the following formula:

Using the formula of two samples mean comparison: -

$n = \{2\sigma^2 (Z\alpha/2+Z\beta)^2\}/ (\bar{x}1 - \bar{x}2)^2$ where, σ= combined standard deviation,

Here, σ1=11, σ2=10

Zα/2 = 1.96 for a 95% confidence level

This set of data was decided by taking reference from the result obtained by Levya et al. (11)

2.5. Intervention

After obtaining clearance from the IRC and NHRC, randomization was conducted, assigning participants to either the Interventional group receiving Flaxseed Capsule 500 mg or the placebo group receiving a look-alike capsule with no therapeutic effect. Both groups were instructed to take their respective capsules twice a day along with the anti-hypertensive drug Amlodipine 5 mg. On the first day of enrollment, before the start of the intervention, the blood pressure of all enrolled subjects was measured. Demographic data and recorded blood pressure were documented on Day 0. Subjects were then given their respective capsules, and the first follow-up was conducted on the 45th day. Finally, subjects were followed up again on the 90th day. The proforma, which included patients' socio-demographic data, blood pressure values, adverse drug reactions (ADR), and drug interactions, was completed. The data were appropriately coded, entered into MS Excel, and subsequently analyzed using SPSS v20 for further analysis.

2.5.1 Subject withdrawal

The study team made every reasonable effort to complete the study. If any subject wished to withdraw from the study at any time, he or she was permitted to do so. Every reasonable effort was made to complete a final assessment.

A subject may withdraw from the study in any of the following circumstances:

1. Serious adverse events
2. Major violation of the protocol
3. Withdrawal of consent
4. Occurrence of any systemic illness during the study period requiring the intake of other drugs
5. Dose modification of equivalent antihypertensive medications required as per the physician's discretion.

2.6 Outcome measures

2.6.1 Primary outcome measures

- To assess the effects of Flaxseed in patients taking antihypertensive drugs.

2.6.2 Secondary outcome measures

- To compare the blood pressure of patients before and after daily consumption of Flaxseed on Day 0, 45th day, and 90th day.
- To analyze adverse effects after daily consumption of Flaxseed.

2.7 Statistical analysis

The intention-to-treat (ITT) population was used for the efficacy analysis. For safety analysis, all randomized participants who took at least one dose of any investigational drug were included. Data collected from the study were coded and evaluated using MS Excel 2013. SPSS 20v was used for per-protocol statistical analysis. Descriptive statistics, including percentages, means, and standard deviations, were calculated and presented graphically and in tables. For inferential analysis, independent t-tests and paired t-tests were applied to determine significant differences between the groups taking both amlodipine and flaxseed and the other groups taking Amlodipine and placebo drugs. Other relevant variables were calculated at a 95% confidence interval, with $p<0.05$.

Procedure-

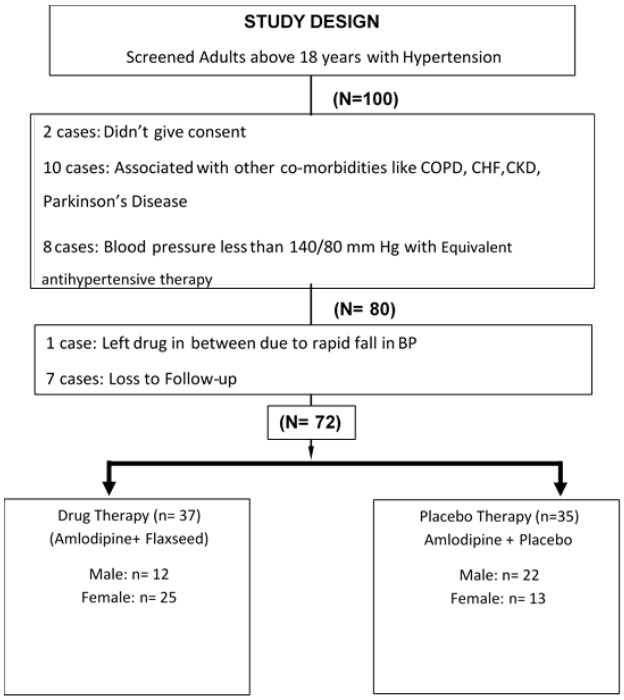

Figure 1: CONSORT Diagram of Study

Results

The study was conducted from September 2020 to September 2021, and it included hypertensive patients above the age of 18 who visited the medicine OPD. A total of 72 hypertensive patients participated in the study, comprising 34 males and 38 females. They were divided into two groups: Drug Therapy group (37 patients) and the Placebo group (35 patients). There were no dropouts after the final enrollment. The mean age of the enrolled patients was 55.38 years, and the mean BMI was 26.53 kg/m2. Six patients experienced side effects such as nausea, constipation, and hypotension due to Flax capsule intake, and they were appropriately managed at the Medicine OPD. Vitals were stable at the time of the OPD visit for all those six patients. Proton pump inhibitor (Omeprazole tablet), Laxative (Lactulose syrup), Oral rehydration therapy, reassurance, and proper counseling to encourage further participation in this study was assured. The detailed results of this Randomized Single Blind Placebo Controlled Trial are presented below.

Table 1: Baseline characteristics of the study population

	Drug Therapy n=37 (51.4%)	Placebo Therapy n=35 (48.6%)
Gender		
Male	11 (29.7)	22 (62.9)
Female	26 (70.3)	13 (37.1)
Age in years		
18-40	3 (8.1)	3 (8.6)
41-60	21 (56.8)	24 (68.6)
>60	13 (35.1)	8 (22.9)
District		
Sunsari	32 (86.5)	26 (74.3)
Morang	0 (0)	5 (14.3)
Siraha	1 (2.7)	2 (5.7)
Saptari	3 (8.1)	1 (2.9)
Dhankuta	1 (2.7)	1 (2.9)
Religion		
Hindu	32 (86.5)	31 (88.6)
Muslim	1 (2.7)	1 (2.9)
Christian	3 (8.1)	2 (5.7)
Kiratis	0 (0)	1 (2.9)
Buddhist	1 (2.7)	0 (0)
Marital status		
Married	37 (100)	35 (100)
Unmarried	0 (0 %)	0 (0 %)
Residence		
Semi-Urban	34 (91.9%)	34 (97.1)
Rural	3 (8.1%)	1 (2.9)
Education		
Literate	17 (45.9%)	25 (71.4)
Illiterate	20 (54.1%)	10 (28.6)
Occupation		
Business	5 (13.5%)	7 (20)
Homemaker	20 (54.1%)	10 (28.6)
Teacher	1 (2.7%)	3 (8.6)
Farmer	5 (13.5%)	8 (22.9)
Service	5 (13.5%)	7 (20)
Sweeper	1 (2.7%)	0
Duration of Hypertension (in years)		
1 to 5	21 (56.8%)	29 (82.8)
6 to 10	6 (16.2%)	3 (8.6)
11 to 15	8 (21.6%)	3(8.6)
16 to 20	1 (2.7%)	0 (0)
>20	1 (2.7%)	0 (0)
Family History		
Yes	17 (45.9%)	20 (57.1)
No	20 (54.1%)	15 (42.9)
Smoking		
Yes	13 (35.1%)	20 (57.1)
No	24 (64.9%)	15 (42.9)
Alcohol intake		
Yes	11 (29.7%)	25 (71.4)
No	26 (70.3%)	10 (28.6)
BMI		
<18.5	1 (2.7%)	0 (0)
18.5-22.9	2 (5.4%)	8 (22.9)
23-24.9	9 (24.3%)	9 (25.7)
25-29.9	17 (45.9%)	14 (40)
>30	8 (21.6%)	4 (11.4)

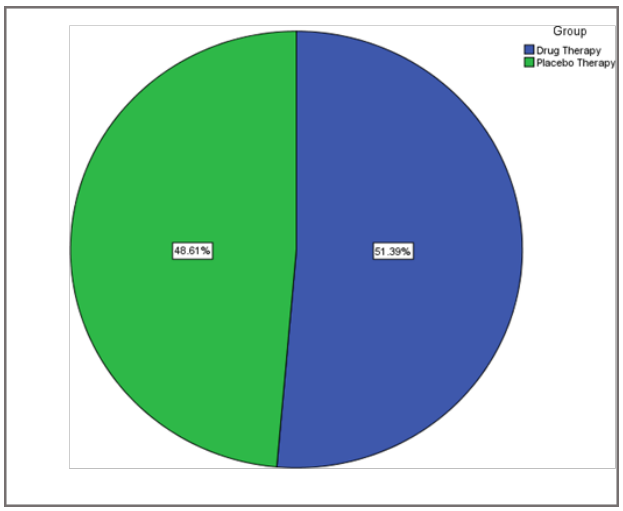

Figure 2: Distribution of Groups in Patients Receiving Intervention

Figure 2 displays the distribution of patients in the intervention study. Out of the total 72 patients, 51.39% received drug therapy consisting of flax capsules with Amlodipine, while 48.61% received placebo therapy consisting of placebo capsules with Amlodipine, as illustrated in Figure 2.

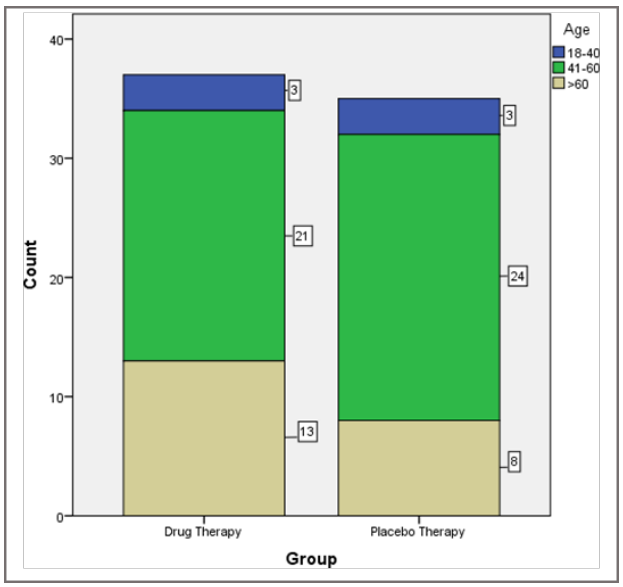

Figure 3: Age distribution among patients receiving intervention

Figure 3 presents the age distribution of the 72 enrolled patients. Among them, 63% fell within the 41-60 years age group, 29% belonged to the above 60 years age group, and only 8% were in the 18-40 years age group. These patients had hypertension and were undergoing antihypertensive drug therapy for a specified duration, as depicted in Figure 3.

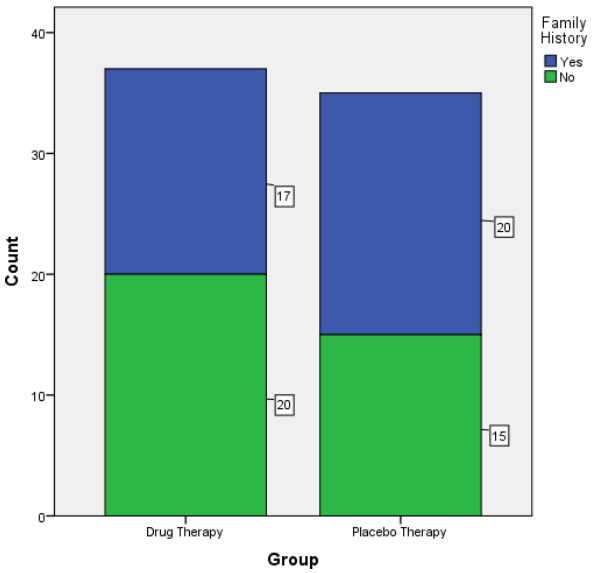

Figure 4: Prevalence of family history among enrolled patients

In Figure 4, the comparison between enrolled patients receiving drug therapy (Flax capsule and Amlodipine together) and placebo therapy (Placebo capsule and Amlodipine together) reveals no significant difference in the prevalence of family history of hypertension. Specifically, 51% of the patients reported a positive family history, while 49% reported a negative family history of hypertension, as depicted in Figure 4.

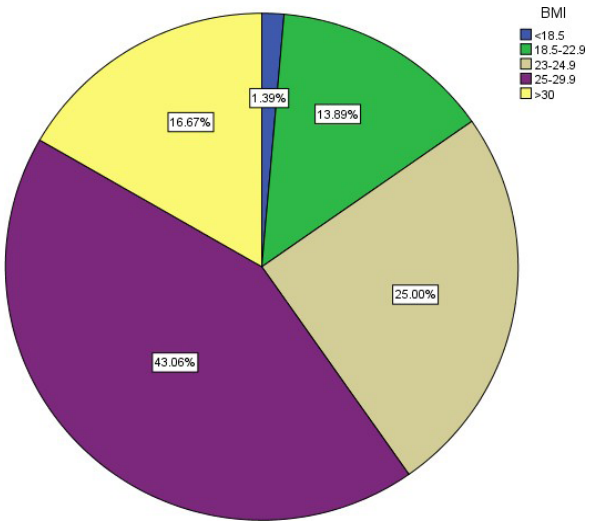

Figure 5: Distribution of BMI among patients receiving the intervention

Given the significant correlation between BMI and SBP/DBP, Figure 5 illustrates the distribution of BMI among the enrolled patients. Approximately 60% of the patients fall within the obese category, followed by 25% in the overweight category, and around 14-15% within the normal category, as depicted in Figure 5.

Systolic Blood Pressure and Diastolic Blood Pressure at Day 0

Table 2: SBP and DBP at Day 0 and Independent – Samples T-test

Group	Drug Therapy	Placebo Therapy	p-value*
SBP Day 0	151.62±13.020 mm of hg	150.86± 10.396 mm of hg	0.671
DBP Day 0	94.86±8.035 mm of hg	90 ± 7.060 mm of hg	0.411

Table 2 summarizes that the SBP and DBP datasets in both groups before the intervention at Day 0 are statistically non-significant.

Table 3: Comparison of SBP and DBP following drug therapy and Amlodipine using Paired-Samples t-test

Data Comparison	Paired Differences	p-Value
SBP Day 0 - SBP Day 45	14.324 ± 12.811	0.001
SBP Day 45 - SBP Day 90	5.405 ± 7.301	0.001
SBP Day 0 - SBP Day 90	19.730 ± 12.799	0.000
DBP Day 0 - DBP Day 45	11.892 ± 7.393	0.003
DBP Day 45 - DBP Day 90	1.892 ± 5.695	0.051
DBP Day 0 - DBP Day 90	13.784 ± 8.284	0.002

Table 3 summarizes that there is a significant reduction in systolic and diastolic blood pressures following drug therapy and Amlodipine when comparing Day 0 to Day 45, Day 45 to Day 90, and Day 0 to Day 90, except for the comparison of DBP Day 45 - DBP Day 90, which appears to be statistically non-significant.

Table 4: Comparison of SBP and DBP following placebo therapy and Amlodipine using Paired-Sample t-test

Data Comparison	Paired Differences	p-Value
SBP Day 0 - SBP Day 45	5.429 ± 7.413	0.001
SBP Day 45 - SBP Day 90	1.714 ± 5.137	0.063
SBP Day 0 - SBP Day 90	7.143 ± 7.101	0.000
DBP Day 0 - DBP Day 45	4.000 ± 6.945	0.001
DBP Day 45 - DBP Day 90	1.143 ± 5.298	0.211
DBP Day 0 - DBP Day 90	5.143 ± 6.585	0.003

Table 4 summarizes the changes in systolic and diastolic blood pressures following placebo therapy and Amlodipine administration. The comparisons were made between Day 0 to Day 45, Day 45 to Day 90, and Day 0 to Day 90. The results indicate a significant reduction in both systolic and diastolic blood pressures, except for the comparison between SBP and DBP at Day 45 and Day 90, which showed no statistically significant difference.

Table 5: Comparison of Systolic and Diastolic Blood Pressure Changes between Drug Therapy and Placebo Therapy Groups over 90 Days

	Drug Therapy (mmHg)	Placebo Therapy (mmHg)	p-value
Systolic Blood Pressure (SBP)			
SBP Day 0	151.62 ± 13.020	150.86 ± 10.396	0.672
SBP Day 45	137.30 ± 6.519	145.43 ± 6.108	0.004
SBP Day 90	131.89 ± 6.163	143.79 ± 6.456	0.001
Diastolic Blood Pressure (DBP)			
DBP Day 0	94.86 ± 8.035	90 ± 7.060	0.416
DBP Day 45	82.97 ± 5.199	86.00 ± 6.945	0.041
DBP Day 90	81.08 ± 4.585	84.86 ± 7.016	0.082

The Systolic Blood Pressure (SBP) decreased gradually during the two follow-up periods on Day 45 and Day 90 in both treatment groups. The magnitude of the decrease was directly proportional to the duration of treatment, as shown in Table 5. The between-group comparison of SBP percentage on the 45th and 90th day using an Independent-Sample T-test was found to be statistically significant.

The diastolic blood pressure (DBP) has decreased in both treatment groups, and the magnitude of the decrease is directly proportional to the duration of treatment, as indicated in Table 6. The between-group comparison of DBP percent on the 45th day using the Independent-Sample T-test yielded a statistically significant result (p=0.04). However, the between-group comparison of DBP percent on the 90th day using the Independent-Sample T-test did not show statistical significance (p>0.05).

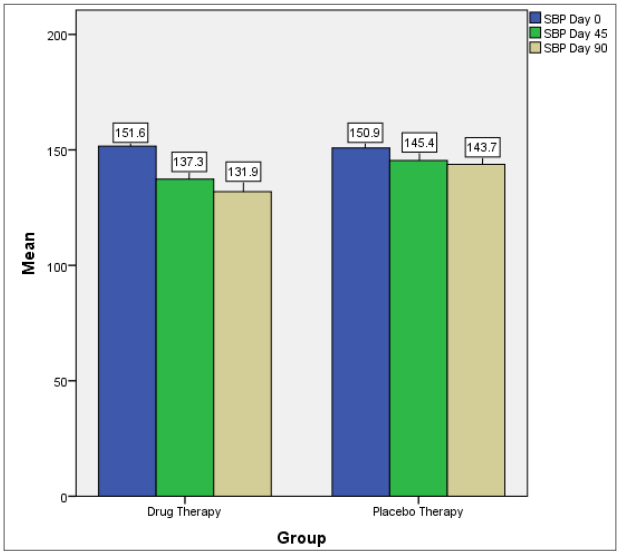

Figure 6: Percentage change in SBP relative to baseline (Day 0) in both treatment groups

In order to facilitate the comparison of systolic blood pressure (SBP) among the groups, we expressed SBP as a percentage relative to the baseline measurement taken on Day 0 (set as 100%). Throughout the study period, SBP decreased in all treatment groups, with the lowest values observed at Day 90 for each group. Notably, when comparing the groups, the reduction in SBP was more significant in the group receiving Flax Capsule and equivalent antihypertensive medications, in comparison to the group receiving Placebo Capsule and equivalent antihypertensive medications, as illustrated in Figure 6.

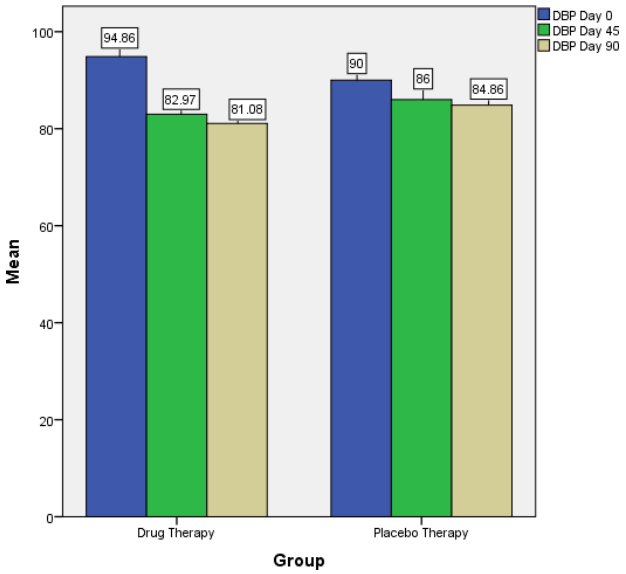

Figure 7: Percentage change in DBP relative to baseline (Day 0) in both treatment groups

To standardize the comparison of diastolic blood pressure (DBP) across the groups, we expressed DBP as a percentage relative to the baseline measurement at Day 0 (set as 100%). Over the course of the study, DBP decreased in all treatment groups, reaching its lowest point at Day 90 for each group. However, when comparing the groups, the decrease in DBP was more pronounced in the group receiving Flax Capsule and equivalent anti-hypertensive medications, compared to the group receiving Placebo Capsule and equivalent anti-hypertensive medications, as illustrated in Figure 7.

After 90 days, the flaxseed group demonstrated a significant reduction in mean Systolic Blood Pressure (SBP) from 151.62 to 131.89 mmHg, equating to a 13.01% decrease versus 4.77 % reduction in placebo group (p-value = 0.001). While there was also a reduction in mean Diastolic Blood Pressure (DBP) from 94.86 to 81.08 mmHg, corresponding to a 14.53% decrease in flaxseed group versus 5.7% reduction in placebo group, this change was not statistically significant (p-value = 0.082).

Discussion

In this study, there were a total of 72 patients, comprising 34 males and 38 females, distributed across different age groups: 18-40 years, 41-60 years, and above 60 years. The mean age of the enrolled patients was 55.38 years, and the mean BMI was 26.53 kg/m^2. Among the total cases, 63% fell within the 41-60 years age group, 29% were above 60 years, and only 8% belonged to the 18-40 years age group. Both sexes were equally represented, with females accounting for 53% and males for 47% of the disease occurrence, resulting in a female-to-male ratio of 1.1:1. A study conducted by Levya et al. in Canada in 2013, titled "Potent Antihypertensive Action of Dietary Flaxseed in Hypertensive Patients," is highly

comparable to our study.[11] Their study reported a similar mean age of presentation (67 years) and a male-to-female ratio of 1:1.

The present study aimed to evaluate the effect of Linum usitatissimum L. (Flax) capsules on systolic and diastolic blood pressure in patients taking anti-hypertensive drugs. The study observed that Flax capsules had a beneficial effect on hypertensive patients. The mean systolic and diastolic blood pressure significantly decreased in patients taking Flax capsules and Amlodipine together compared to those taking Placebo capsules and Amlodipine together.

Side effects such as nausea, constipation, and hypotension occurred in 6 patients, and they were appropriately managed at the Medicine OPD. Fortunately, all these patients completed their assigned interventions. Notably, the study conducted by Levya et al. did not address these particular side effects.

Around 80% of the patients were from Sunsari district, while the remaining 20% were from nearby districts. This hospital serves as the tertiary care center for the eastern region of Nepal, explaining the geographical distribution. The religious and ethnic composition of the patients aligned with the regional demographics, with 87% being Hindu, and the remaining 13% comprising Christians, Buddhists, Kiratis, and Muslims.

There was no significant difference in the family history of hypertension among the groups, with 51% reporting a positive family history and 49% reporting a negative family history of hypertension. However, this finding does establish a family history as one of the risk factors for hypertension. Smoking and alcohol consumption were reported by 46% and 50% of the patients, respectively.

Since BMI is significantly correlated with SBP and DBP, the figures demonstrate that approximately 60% of the enrolled patients fell within the obese category, followed by 25% in the overweight category, and around 14-15% within the normal category.

In the case of loss to follow-up, patients were contacted using the contact numbers recorded in the proforma.

In our study, the combination of Flax capsules and anti-hypertensive drugs resulted in a significant reduction ($p<0.05$) in SBP by the 45th day and at the end of the 90th day, compared to the combination of placebo capsules and equivalent anti-hypertensive drugs. The reduction in DBP was significant ($p<0.05$) by the 45th day but became statistically non-significant ($p>0.05$) after the 90th day between the two groups. Approximately 80% of patients from both groups maintained the same dose of anti-hypertensive medication throughout the trial. It has been proposed that Flax capsules lower blood pressure by altering circulating oxylipins through α-linolenic acid-induced inhibition of soluble epoxide hydrolase.[19]

Similarly, various studies have shown the effect of different forms of flax on blood pressure in hypertensive patients. Flaxseed, containing ALA, may exhibit its anti-hypertensive potential through its anti-inflammatory effect. In a randomized, controlled, crossover trial, 23 hyperlipidemic patients were provided with a high-ALA diet, high linoleic acid diet, or a typical western diet for 6-week periods each. The high-ALA diet notably reduced peripheral blood mononuclear cell production of interleukin-6, interleukin-1, and tumor necrosis factor-alpha compared to the high linoleic acid diet.[20] Additionally, ground flaxseed consumption reduced pro-inflammatory oxylipins in the plasma of older adults after 4 weeks.[21] Essential hypertension has been theorized to result from inflammation and endothelial dysfunction, leading to an imbalance between endothelial-derived vasoconstrictive factors and vasodilative factors. If ALA has anti-inflammatory effects, it is likely to prevent the inflammation-induced imbalance of molecules that regulate vascular tone. ALA may also influence inflammation and blood pressure by altering the oxylipin profile.[22]

Limitations

This research had certain limitations and shortcomings. Firstly, the study was conducted over a relatively short period, which limits our understanding of the long-term effects of flax capsules. A longer duration would have provided more comprehensive insights. Secondly, the sample size was small, restricting the generalizability of the results to larger populations. Including a larger number of participants in future studies would improve statistical power and enhance the validity of the findings. Also, there was unequal distribution of participants based on their gender and religion in both groups, as the sample was selected through randomization during the time of the COVID pandemic. Lastly, the lack of medical staff supervision for the intake of flax capsules raises concerns about consistency and adherence to the prescribed regimen. This may introduce variability and affect the overall effectiveness of the intervention. The quality of the intervention drug could not be measured due to the unavailability of required funds and technologies. Similarly, the effect of flaxseed on lipid profile, blood glucose, and various other inflammatory bio-markers could not be studied due to the limitation of time and funds.

To overcome these limitations, further research is needed. Larger-scale trials with longer durations and closer medical supervision would provide more robust evidence and address the limitations identified in this study.

Conclusion

Based on observation of our study, the inclusion of flaxseed supplements into the treatment regimen for hypertension, in conjunction with antihypertensive medications, led to a notable reduction in blood pressure levels Based on these findings, it can be concluded that the administration of flax capsules alongside antihypertensive drugs in patients with hypertension can be both effective and safe in maintaining blood pressure levels, consequently reducing the risk of cardiovascular diseases. However, further multicentric randomized clinical trials with greater sample sizes for longer intervention periods and follow-up duration are necessary to estimate effects with precision and negative effects become less likely.

Abbreviations

ADRs - Adverse Drug Reactions
ALA - Alpha-linolenic acid
BPKIHS - B.P. Koirala Institute of Health Sciences
BMI - Body Mass Index
DBP - Diastolic Blood Pressure
HIV - Human Immunodeficiency Virus
IRC - Institutional Review Committee
ITT - Intention-to-treat
MS - Multiple Sclerosis
NCDs - Non-communicable Diseases
NHRC - Nepal Health Research Council

OPD - Out Patient Department

SBP - Systolic Blood Pressure

SPSS - Statistical Package for the Social Sciences

Author contributions

Conceptualization: RV.

Methodology: RV, GPR, BK, SS, UC, AS.

Data analysis: RV, RV, PK.

Writing original draft: RV, BS,

Writing review and editing: RV, BS, BK, GPR.

Supervision BS, GPR, SS, BK.

Conflict of interest

The authors declare no conflict of interest.

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Ethical statement

This research has been approved by the Institutional Review Committee at BPKIHS, Dharan (Reference.no.: - 347/077/078-IRC) and Nepal Health Research Council, Kathmandu-Nepal (Ref.no. - 2608).

Data availability

The data will be made available by the corresponding author upon reasonable request.

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