STUDY ON ANTIHYPERTENSIVE EFFECT OF MODIFIED TMF-28 IN UNCOMPLICATED HYPERTENSIVE PATIENTS

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INTRODUCTION

Hypertension affects approximately one billion individual worldwide. It is the most common cardiovascular disorder affecting 20% of adult population worldwide. It is also an important public health problem of global dimensions, both in the developed and developing world (Newby, Grubb and Brabury, 2007).

.1. Justification

In Myanmar, hypertension is one of the six leading diseases of morbidity. Patients with uncomplicated hypertension are asymptomatic or mildly symptomatic and they only notice that they have hypertension during medical check-up or when seeking management for other diseases (Moe-Kyaw-Myint, *et. al.*, 2010).

There are many anti-hypertensive drugs currently in use. They are relatively expansive and have side effects of one form or another. For example, nifedipine and amlodipine can cause tachycardia and swelling of legs, atenolol and diltiazem cause bradycadia while ACE inhibitors have side effects such as cough and angioedema (Min-Han, 2007).

LITERATURE REVIEW

Traditional Medicine Formulation No. 28 (ThetyinnkalatHsay)

The Traditional Medicine Formulation -28, ThetyinnkalattHsay is composed of nine plant ingredients and one mineral/salt. *Croton oblongifolius* (root), Thetyinngyee, is the major ingredient of the formulation. Half of the drug is composed of Thetyinngyee and the rest of half is occupied by the rest of 8 plant ingredients and mineral (roasted salt).

Scientific Name	Myanmar Name	Amount in g/100 g
Major plant		
Croton oblongifolius	Thetyinngyee (Root)	50.0
Other ingredients		
Capparissepiaria	Hsoogauknet (bark)	5.6
CrataevareligiosaForst.	Kadet (bark)	5.6
Piper nigrum	NgayokeKaung (fruit)	5.6
OsyrisWightiana	Zaunggyan (fruit)	5.6
Piper longum	Peikchinn (fruit)	5.6
Sapium sp.	Awle (Stem)	5.6
Zingiberofficinale)	Gyin (Rhizome)	5.6
	Hsaypale (Root) Unidentified	5.6
Mineral/Salt ingredient		
Roasted Salt	Hsah Law	5.6

(တိုင်းရင်းဆေးပညာဦးစီးဌာန, 1990).

2.2. Modified TMF-28

Modified TMF-28 is formulated by replacing roasted salt with *GisekiapharnaceoidesLinn.*(Kantkalar). Instead of using roasted salt, replacement of Kant-ka-lar forms the new formulation which has similar efficacy to that of TMF-28. It can be used for Vata disease by regularizing pathway of air (Vayu) to run down.

Ingredient to be substituted

Gisekiapharnaceoides Linn. (the whole plant)	Kant-ka-lar	5.6

Ingredient not to be added

Roasted Salt	Hsah-Law	5.6

***Croton oblongifolius* (Thetyinngyee)**

***Piper nigrum* (NgayokeKaung)**

***Piper longum* (Peikchinn)**

***Zingiberofficinale* (Gyin)**

CrataevareligiosaForst **(Kadet) Bark**

***GentianaKurroo* (Hsaypale) Root**

***Sapium sp.* (Awle) (Stem)**

***Capparissepiarie*(Hsoogauknet) (Bark)**

***Osyriswightiana* (Zyaunggyan) (Fruit)**

Gisekiapharnaceoides Linn. **Kantkalar**
(The whole plant)

2.2.3. Dosage

2 g single oral for adult. (7 tablets, 300 milligram/tablet)

2.2.4. Toxicity

Not toxic effect was observed on acute administration (The LD_{50}in mice, rats and rabbits being greater than 3.2, 1.6, and 0.8 g/kg respectively.In clinical trial of glucose lowering effect conducted by DMR (Upper Myanmar) in 2010, for safety of TMF-28, they measured liver enzymes, (SGOT, SGPT and ALP), serum bilirubin, serum creatinine and ECG at pre-invention and post-intervention periods.

It was observed that there were no changes in ALP, serum creatinine and ECG (Tin-Tin-Wynn, *et. al*., 2010). Therefore, TMF-28 was found to be a safe drug during study period, which needs to be further evaluated for its long term safety and efficacy (WHO, 2000).

Traditional medicine pharmacological aspects

It's actions in traditional wise included promote digestion, increase motion, purify impurities in body, suppress wind phlegm, cure neuralgia, relieve tingling and numbness of limbs, all types of paralysis, allergy, urticaria, inflammation, diabetes insipidus, and kill germs.

(1) Rasa (Taste)	- Hot, bitter, spicy
(2) Dhatu Rasa	- Ohna (Ushnatezo) - vata (vayu), arkasa (akarsh)
(3) Vi PaKa	- Hot and spicy
(4) Gu Na	- Ohna (ushnatezo) (caused by heat) - Lu kha (dryness) - La hu (lightness) - Tikkha (sharp and rapid)

(5) Vi RiYa - Ohna (ushnatezo) (caused by heat)
- Lu kha (dryness)
- La hu (lightness)
-Tikkha (sharp and rapid)

(6) Kicca (Kitsa) **(Functions & effects)**
-Digestion, regular defecation,
-Exploring arkasa (Akarsh), purify blood
-It is indicated to treat wind phlegm disease, paralysis, hemiplegia, pruritis, inflammation, pain, polyuria.

(7) Pa Bar Wa **(Extraordinary effect)**
Can be used for wind and blood disorders. Eliminating excessive coldness and making Vayu descendand exploring arkasa (Akarsh)

(တိုင်းရင်းဆေးပညာဦးစီးဌာန,1990).

2.3. Normal Arterial Blood Pressure

The brachial arterial blood pressure of young adults in the sitting or lying position at rest is approximately 120/70 mmHg. Since the arterial pressure is the product of the cardiac output and the peripheral resistance, it is affected by conditions that affect either or both of these factors.

Emotion increases the cardiac output and peripheral resistance, and about 20% of hypertensive patients have blood pressures that are higher in the doctor's office than at home, going about their regular daily activities (white coat hypertension).

Blood pressure normally falls by as much as 20 mmHg during sleep. This fall is reduced or absent in hypertensive patients. Consequently, normal are sometimes called "dippers" and hypertensive are called "non-dippers" (Ganaung, 2005).

Measurement of blood pressure by auscultation National Institute of Health and Clinical Excellence guideline (2006)

Blood pressure is measured by auscultation method as follow;The brachial pulse is palpated in the antecubital fossa of that arm. The cuff is rapidly inflated to 20 mmHg above the point where the brachial pulse disappears. The cuff is then deflated and noted the pressure at which the brachial pulse re-appears: the approximate systolic pressure. Re-inflate the cuff to 20 mmHg above the point at which the brachial pulse disappears. Using one hand, the stethoscope is placed over the brachial artery ensuring complete skin contact with no clothing in between. The cuff is slowly deflated at 2-3 mmHg per second listening for Korotkoff sounds.

Phase I: The first appearance of faint repetitive clear tapping soundsgradually increasing in intensity and lasting for at least two consecutive beats. This is noted as the systolic pressure.

Phase II: A brief period may follow when the sounds soften or 'swish'.

Phase III: The return of sharper sounds becoming crisper for a shorttime.
Phase IV: The distinct, abrupt muffling of sounds, becoming soft and blowing in quality.
Phase V: The point at which all sounds disappear completely. This is noted as the diastolic pressure.

2.3.2. Methods of blood pressure measurement

Methods of blood pressure measurement are important considerations in clinical trials. Blood pressure measurement results vary not only individually but also in the same person measured at different arms at the same time. Moreover, blood pressure varies at heart beat by beat and time to time. Different measurement readings are produced by different observers in the same person. Blood pressure also differs with diurnal rhythm. It rises after waking and falls down after mid-night. Therefore, time of measurement is another important consideration in anti-hypertensive drug trial.

Clinic blood pressure measurement can reveal only one time point reading. It can also give rise the white coat hypertension. Twenty percent of the hypertensions are due to white coat effect (WCE) (Paolo Platini, 2000).

Definition of hypertension (WHO/ISH,2007)

Hypertension is defined as a systolic blood pressure of 140 mmHg or greater and/or a diastolic blood pressure of 90 mmHg or greater in subjects who are not taking antihypertensive medication.

In the majority of people, no underlying cause for hypertension can be identified. Such cases of hypertension are said to be primary (or essential), in contrast to approximately 5% of cases where secondary causes such as renal, vascular or endocrine disease may be found.

Primary hypertension is a multi-factorial disease with a number of recognized aetiological factors, several of which are usually present in an individual patient.

Target organ

Target organ damages due to complications of hypertension are:

Heart -Left ventricular hypertrophy
Angina or prior myocardial infarction
Prior coronary revascularization
Heart failure

Brain -Stroke or transient ischemic attack

Chronic kidney disease

Peripheral arterial disease

Retinopathy

(Newby, Grubb and Bradbury, 2007)

Mortality

Treatment of Hypertension
Traditional medicine for treatment of hypertension

OBJECTIVES

3.1. General Objective

To study the antihypertensive effect of Myanmar Traditional Medicine (modified TMF-28) in uncomplicated hypertensive patients.

3.2. Specific Objectives

1. To determine the blood pressure of uncomplicated hypertensive patients before treatment (day 0).
2. To determine the blood pressure of uncomplicated Hypertensive patients during treatment and after treatment.
3. To compare the effect of antihypertensive activity of modified traditional medicine formulation 28 at day 0 (before treatment) with those at day 7, 13, (during treatment) and day 14 (at the end of treatment).

METHODOLOGY

4.1. Study Design

Study was conducted by self-controlled clinical trial which is also called modified randomized clinical trial.

4.2. Study Area

Monasteries were chosen randomly at Mandalay Aung Myay Thar San Township as KyaungHtaiMonastery Training School, Sanbuddhe Monastery, Damma wiharriMonastery.

4.3. Study Population

All uncomplicated hypertensive patients who fulfilled the inclusion from KyaungHtai Monastery Training School, Sanbuddhe Monastery, Damma wiharri Monastery at Aung MyayThar San Township, Mandalay.

4.4. Selection Criteria

Inclusion criteria

1. The patients with the age of 30 to 70 years old
2. Uncomplicated hypertensive patients
   Patients with stage I and stage II hypertension according to JNC criteria.

Stage I (mild hypertension); 140/90 to 159/99 mmHg.

Stage II (moderate hypertension); 160/100 to 179/109 mmHg

3. The patients who gave informed consent.

Exclusion criteria

1. The patients who had been taking any anti-hypertensive drug
2 .The patients with other diseases such as diabetes, ischaemic heart disease
3. The patients with severe hypertension (180/110 mmHg and above)
4. The patients who did not want to participate in the study.
   of severe side effects (including drug allergy)

5. Pregnant and lactating mothers.
6. The patient with peptic ulcer.
7. The patient with bleeding tendency.
8. The subjects with white coat hypertension

Withdrawal criteria

1. Subject's request
2. Patient became ill or had complications of hypertension
3. Development

4.5. Study Period

The study was conducted for 2 weeks and three days covering the period from May to October, 2012.

4.6 Sample Size Calculation

Confidence Interval is 95%, Power 80%, Estimation of treatment effect is 60%.
Then required sample size is 22 to add drop out, sample size was 30 calculated by Epi-Info version 3.4.1.

4.7 Sampling Method

Randomization and screening of patients were done. At first, the blood pressure of all Buddhist monks and nuns living from KyaungHtai Monastery Training School, Sanbuddhe Monastery, Dammawiharri Monastery were measured in three consecutive visits.

A total 321 Buddhist monks and nuns were examined. Secondly, all of monks and nuns over 30 years were checked for hyper-tension. Then, he patients were selected according to inclusion criteria. A total of 22 Buddhist monks and nuns were enrolled in the study.

4.8 Materials

Apparatus for blood pressure measurement used in the study was validated with international gold standard mercury sphygmomanometer.

A brand new standardized sphygmomanometer of investigator must be regarded as random 0 standard sphygmomanometer.

Preparation of drug and training
Preparation of drug

4.9.3. Baseline period

It was taken for 3 days. Total of 22 hypertensive patients were observed for 3 consecutive days as baseline time without giving any antihypertensive drugs. During this period, baseline data blood pressure was recorded to describe the blood pressure of before treatment in every morning by investigator.

4.9.4.Drug administration period

After the baseline period, the patients had to take antihypertensive drug orally for 2 weeks.The investigator directly gave the test drug to the subjects with the dose of seven tablets (300 milligram of modified ThetyimmkalatHsay TMF-28 in one tablet) orally for three times a day. Then the blood pressure of individual subjects was measured and recorded daily in the morning before meal.

Data collection procedure

History taking and physical examinations were done by the observer and those data were recorded by annexes. Daily blood pressure readings were also recorded into the blood pressure record form (Annex-2).

All subjects were seen by the investigator and detailed history and thorough physical examination were done. BP was measured daily for three days to confirm that they had hypertension. The patients were selected according to inclusion criteria. Only those patients who gave voluntary informed consent were checked up for the study. During the trial period, the patients were advised not to take alcohol, smoking and salty diet. The heart rate and BP were measured after 15 minutes rest at supine position and then measured after 2 minutes in study.

RESULT

In this study, a total of 22 patients with uncomplicated hypertension were studied. They were observed on the day 0 (baseline) (before treatment) and day 7, day 13 (during treatment) and day 14 (at the end of treatment). The youngest age was 30 years and the oldest patient was 63 years.

Mean blood pressure of patients on Day 0 (for baseline)

Mean blood pressure of patients on Day 0 (for baseline)

Mean blood pressure patients for baseline (3 consecutive days)were shown in Table 7 and Figure 39. On Day 0, baseline mean SBP was 134.5 mmHg and DBP was 94.01 mmHg.

Mean blood pressure for baseline(3 consecutive days)

Baseline (1st to 3rd Day)

	Mean Systolic BP (mmHg)	Mean Diastolic BP (mmHg)
1stDay	134.63	94.05
2ndDay	134.32	92.86
3rdDay	134.5	95.14
Mean (Average) BP for Day 0	134.48	94.01

Blood pressure of individual patients on Day 0 (for baseline)

Sr.	Code No.	SBP (mmHg)	DBP (mmHg)
1`	1	132.66	90
2	2	130	94.33
3	3	136.66	93.33
4	4	133.33	90
5	5	130.33	95
6	6	136	96.67
7	7	126	91
8	8	135	96.67
9	9	130	91.67
10	10	133.33	100
11	11	146	95.33
12	12	136.66	98.33
13	13	134.33	92.67
14	14	140	91.67
15	15	141.66	103.3
16	16	136.66	93.33
17	17	130	90
18	18	128.33	90
19	19	130	93.33
20	20	143.33	101.7
21	21	135	90
22	22	133.33	90

Blood pressure of patients on Day 7

Blood pressure of individual patients on Day 7

On Day 7,SBP of 95.4 % of patients and DBP of all patients were decreased in comparison with baseline level.

Systolic blood pressures for individual patients on Day 7

Sr.Code	Day 0 (Base Line Average)	Day 7SBP (mmHg)S	BP(mmHg)
1	1	133	120
2	2	130	120
3	3	137	125
4	4	133	120
5	5	130	120
6	6	136	130
7	7	126	130
8	8	135	130
9	9	130	120
10	10	133	120
11	11	146	120
12	12	137	130
13	13	134	130
14	14	140	130
15	15	142	125
16	16	137	120
17	17	130	130
18	18	128	110
19	19	130	100
20	20	143	120
21	21	135	110
22	22	133	105

Diastolic blood pressure (mmHg) of individual patients on Day 7

Sr.	Code	Day 0	Day 7
1	1	90	80
2	2	94.33	80
3	3	93.33	90
4	4	90	80
5	5	95	90
6	6	96.66	90
7	7	91	90
8	8	96.66	90
9	9	91.66	80
10	10	100	90
11	11	95.33	85
12	12	98.33	90
13	13	92.66	90
14	14	91.66	90
15	15	103.33	88
16	16	93.33	80
17	17	90	80
18	18	90	75
19	19	93.33	75
20	20	101.66	80
21	21	90	70
22	22	90	70

Mean blood pressure of patients at on Day 7

It was found that mean SBP was 134.485 mmHg and mean DBP was 94.015 mmHgat baseline level assessment. Mean SBP and mean DBP on Day 7 were shown in Table. The patients received modified TMF drug on Day 7.

Mean SBP significantly fell down from 134.485 mmHg (at baseline) to 121.14 mmHg on Day 7 ($p<0.01$). The mean DBP was also significantly fell down from 94.015 mmHg at baseline to 82.23 mmHg on Day 7 ($p<0.01$).

Mean blood pressure of patients on Day 7

Day	Mean Systolic BP (mmHg)	Mean Diastolic BP (mmHg)
Baseline	134.48	94.01
Day 7	121.14	83.32

Blood pressure of individual patients on Day 13

Blood pressure of individual patients on Day 13

On Day 13, SBP fell down from baseline level to lower level in 95% of patients. There was no SBP change of patients with code No. 5 and code No 7. A little reduction of SBP was observed in patients with code No.10 and code No.18. DBP fell down from baseline level to lower level in all patients. However, little reduction of DBP was observed in patients with code No.3, 4,13,14 and 15.

Systolic blood pressure of individual patients on day 13

Sr.	Code	Day 0 (Baseline Average) SBP (mmHg)	Day 13 SBP (mmHg)
1	1	132.66	125
2	2	130	125
3	3	136.66	110
4	4	133.33	120
5	5	**130.33**	**130**
6	6	136	123
7	7	126	130
8	8	135	130
9	9	130	120
10	10	133.33	130
11	11	146	120
12	12	136.66	130
13	13	134.33	120
14	14	140	130
15	15	**141.66**	**142**
16	16	136.66	128
17	17	130	125
18	18	128.33	125
19	19	130	110
20	20	143.33	120
21	21	135	110
22	22	133.33	110

Diastolic blood pressure (mmHg) **of individual patients on Day 13**

Sr.	Code	Day 0	Day 13
1	**1**	**90**	**85**
2	**2**	**94.33**	**85**
3	**3**	**93.33**	**90**
4	**4**	**90**	**88**
5	**5**	95	85
6	6	96.66	90
7	7	**91**	**90**
8	8	96.66	90
9	9	91.66	85
10	10	100	80
11	11	95.33	85
12	12	98.33	90
13	13	**92.66**	**90**
14	14	**91.66**	**90**
15	15	**103.33**	**100**
16	16	93.33	80
17	17	90	70
18	18	90	85
19	19	93.33	80
20	20	101.66	85
21	21	90	70
22	22	90	70

Mean blood pressure of patients on Day 13

The mean SBP of baseline value was 134.485v mmHg and mean DBP at baseline was 94.015mmHg. The mean SBP on day 13 after administration of modified drug was 123.31 mmHg. It was significantly decreased ($p<0.01$) in SBP from baseline to day 13. The mean DBP on day 13 after administration of modified drug was 84.68 mmHg. It was significantly decreased ($p<0.01$) in DBP from baseline to day 13.

Mean blood pressure of patients on Day 13

Day	Mean Systolic BP (mmHg)	Mean Diastolic BP (mmHg)
Baseline	134.48	94.01
Day 13	123.31	84.68

Blood pressure of patients on Day 14

Blood pressure of individual patients on Day 14

On Day 14, SBP fell down from baseline level to lower level in 91% of patients. The SBP of patients with code No.5 and code No. 7 was not changed on day 14.But little reduction of SBP was observed in patient code No.3.

The DBP fell down from baseline level to lower level in all patients. In addition a little reduction of DBP was observed in patient code No.3, 7 and code No.14.

Systolic blood pressure of individual patients on day 14

Sr.	Code	Day 0 (Baseline Average) SBP (mmHg)	Day 14 SBP (mmHg)
1	1	132.66	120
2	2	130	120
3	3	**136.66**	**133**
4	4	133.33	125
5	5	**130.33**	**130**
6	6	136	130
7	7	**126**	**130**
8	8	135	130
9	9	130	125
10	10	133.33	125
11	11	146	120
12	12	136.66	125
13	13	134.33	125
14	14	140	130
15	15	141.66	133
16	16	136.66	120
17	17	130	120
18	18	128.33	120
19	19	130	100
20	20	143.33	130
21	21	135	100
22	22	133.33	105

Diastolic blood pressure of individual hypertensive patients on Day 14

Sr.	Code	Day 0 (Baseline Average) DBP (mmHg)	Day 14 DBP (mmHg)
1	1	90	80
2	2	94.33	80
3	3	**93.33**	**90**
4	4	90	85
5	5	95	85
6	6	96.66	90
7	7	**91**	**90**
8	8	96.66	90
9	9	91.66	80
10	10	100	85
11	11	95.33	85
12	12	98.33	80
13	13	92.66	85
14	14	**91.66**	**90**
15	15	103.33	95
16	16	93.33	80
17	17	90	80
18	18	90	80
19	19	93.33	70
20	20	101.66	85
21	21	90	70
22	22	90	75

Mean blood pressure of patients on day 14 (at the end of treatment)

The mean SBP and mean DBP at baseline were 134.48 mmHg and 94.015 mmHg. The mean SBP on day 14 was 122.54 mmHg and mean DBP on Day 14 was 83.18 mmHg. So, the blood pressure of the patients tended to reduce on 14 days after treated with modified TMF-28. The mean SBP significantly decreased ($p<0.01$) from 134.485 mmHg at baseline to 122.54mmHg on Day 14. In addition, the mean DBP also significantly decreased ($p<0.01$) from 94.015 mmHg at baseline to82.83 mmHg on Day 14.

.Mean blood pressure of patients on day 14 (at the end of treatment)

Day	Mean Systolic BP (mmHg)	Mean Diastolic BP (mmHg)
Baseline	134.48	94.01
Day 14	122.55	82.83

Mean blood pressure and p. valve on Day 0 (baseline), Day 7, Day 13 and Day14

Mean blood pressure and p valve on Day 0 (baseline), Day 7, Day 13 and Day14

Day	Mean Systolic BP (mmHg)	p value	Mean Diastolic BP (mmHg)	p value
Day 0 (Baseline)	134.48		94.01	
Day 7	121.14	<0001	83.32	<0001
Day 13	123.31	<0001	84.68	<0001
Day 14 End of treatment	122.55	<0001	82.83	<0001

Changes in Heart Rate of Patients

Changes in Heart Rate of Patients

Minimum = 67 beats /minutes Maximum = 81beats /minutes
Mean = 74.175beats /minutes
Mean heart rate at baseline was 74.175beats /minutes shown in Table .
After treatment with modified TMF-28, heart rate did not significantly changed (P>0.01). Therefore, the modified TMF-28 had no significant effect on heart rate during this study period.

Paired samples test for heart rate of patients at baseline & end of treatment

	HR Before	***HR after***
Mean	74.175	74.634
Variance	12.507	21.219
Observations	22.000	22.000
Pearson Correlation	0.498	
Hypothesized Mean Difference	0.000	
Df	21.000	
t Stat	**-0.503**	
P(T<=t) one-tail	**0.310**	
t Critical one-tail	1.725	
P(T<=t) two-tail	0.620	
t Critical two-tail	2.086	

DISCUSSION

In this study, a total of 22patients with uncomplicated hypertension were investigated. This was the clinical trial done in Buddhist monks of Mandalay KyaungHtai Monastery Training School, Sanbuddhe Monastery and Dammawiharri Monastery with the aim to determine the antihypertensive effect of modified Myanmar traditional medicine formulation-number 28 (TMF-28).

At first, the blood pressure of all Buddhist monks and nuns living from Mandalay Kyaung Htai Monastery Training School, Sanbuddhe Monastery, Dammawiharri Monastery were measured in three consecutive visits. A total of 321 Buddhist monks and nuns were examined. Screening procedure was done for three days. During those days, the normal subjects were excluded. Secondly, all of monks and nuns over 30 years were checked for hypertension. Then, the patients were screened according to inclusion criteria.

A total of 22 Buddhist monks and nuns were enrolled in the study. History taking and physical examination were done by observer and data were collected in the record forms (Annex-1). Daily blood pressure readings were also recorded into the blood pressure record form (Annex-2).

Apparatus for blood pressure measurement used in the study was validated with international gold standard mercury sphygmomanometer. Baseline data (age, sex, body weight, heart rate and BP) were investigated and recorded.

Matured and dried ingredients of parts of medicinal plants were collected and carefully washed them to remove dust and any foreign materials. The dried parts of medicinal plants were powdered with an electric grinder and made into 300 mg tablets with a ZP 33 B rotator tablet press machine at traditional medicine factory, Mandalay.

House officers and trained traditional medicine officers from Acupuncture unit of Traditional Medicine Teaching Hospital, Mandalay were trained for data collection.

They were guided how to give medicine to the patients (according to their code No.) and to ensure that the patients took the drug 3 times/day at 6:00 a.m., 2:00 p.m. and 10:00 p.m. for 2 weeks. The BP of day 0 before treatment was compared with the BP of day 7, day 13(during treatment) and day 14 (at the end of treatment)to evaluate the effect of antihypertensive activity of modified TMF-28.

The blood pressure of selected individual patient was measured in three consecutive days for the baseline BP. The average of BP of individual patient in three days was taken as baseline BP (BP of day 0). The day 0 mean systolic blood pressure of patients was 134.48 mmHg and that of mean diastolic blood pressure was 94.01 mmHg (Table 7).

On Day 7, the reductions in SBP of 95.4 % of patients and DBP of individual patients were observed .The SBP and DBP of individual patients fell down from baseline level to lower level. The values of mean SBP and mean DBP on day 13 and that of on day 0 were calculated by paired t test. Mean SBP fell down from baseline BP(134.48 mmHg) to 123.31 mmHg ($p<0.01$). The mean DBP on day 7 was decreased from baseline BP(94.01mmHg) to 85.33 mmHg ($p<0.01$). Thus, the reduction of both SBP and DBP on day 7 was significant.

On Day 13 (during treatment),the reductions of SBP and DBP were observed in individual patients. The SBP fell down from baseline level to lower level in 95% of patients. The DBP of individual patient fell down from baseline level to lower level.

The values of mean SBP and mean DBP on day 13 and that of on day 0 were calculated by paired t test. Mean SBP fell down from day 0 BP (134.48 mmHg) to 125.56 mmHg ($p<0.01$). The mean DBP fell down from day 0 BP (94.01 mmHg) to 84.68 mmHg ($p<0.01$). Thus, the reduction of both SBP and DBP on day 13 was significant.

On Day 14(at the end of treatment), the reductions of SBP and DBP was observed in individual patients. The SBP fell down from baseline level to lower level in 91% of patients.

The DBP of individual patients fell down from baseline level to lower level. The values of mean SBP and mean DBP on day 14 and that of on day 0 were calculated by paired t test. It was also observed that mean SBP fell down from baseline level 134.48 mmHg to 122.55 mmHg ($p<0.01$) on day 14. The mean DBP fell down from 94.01 mmHg to 83.18 mmHg ($p<0.01$) after treatment with modified TMF-28.

Thus modified TMF-28 had significant blood pressure lowering effect (both SBP and DBP) on uncomplicated hypertensive patients in this study.

At the end of study, the following laboratory data were rechecked. Blood for creatinine was done before and after the study period. Investigation for blood sugar was done to detect presence of diabetes mellitus among the participants for exclusion criteria.

Investigation for blood cholesterol was done before and after study period. There were no significant changes in body weight and serum cholesterol by administration of TMF-28 for 14 days in this study.

In addition, the heart rate was also not significantly changed in this study ($p>0.01$).It was also found that there was no special complaint by taking modified TMF-28 in the patients. Thus, it was observed that modified TMF-28 had no side effects in the study period of 2 weeks.

Kant Kalar, (*Gisekiapharnaceoides Linn.*) was substituted for roasted salt in modified TMF-28. Kant Kalar has bitter taste. It has descending function of Vata and regularizes defecation and urination, eliminates excessive Prithvi and Apo. Kant-Kalar was easily available in locality with low cost. Modified TMF-28 was prepared by adding Kant-Kalar and it has hot, bitter and spicy taste.

According to Traditional Medicine pharmacological aspect, these tastes subdue the excessive coldness and eliminate excessive Apo and excessive internal Prithvi (တိုင်းရင်းဆေးပညာဦးစီးဌာန ,1990).

Hypertension is commonly caused by inter-locked of air, coldness, excessive internal Prithvi and excessive Apo (dampness)(တိုင်းရင်းဆေးပညာဦးစီးဌာန, 2008). Tha-Bar-Wa-Dhanma-Saya-Than described that hypertension can be named as cold blood rising disease in traditional medicine point of view. It was evidenced that objectives of treatment on hypertension are to relieve coldness, to let air (Vayu) run down, to regularize defecation and urination and to explore Arkarsa. Modified TMF-28 had the above mentioned effects to treat hypertension.

Therefore, this study indicated that modified TMF-28 had antihypertensive effect on mild and moderate hypertension without complications. Thus, modified TMF-28 could be assumed as an effective drug for treatment of hypertension.

CONCLUSION

This study observed that modified TMF-28 had significant blood pressure lowering effect for the treatment of uncomplicated mild and moderate hypertension.

There was no obvious side effects and no special complaints of the subjects in this study.

RECOMMENDATION

According to the findings of this study, the following points were recommended to treat hypertension with modified TMF-28.

1. Modified TMF-28 was effective in reduction of high blood pressure in both sexes.
2. TMF-28 should be used for mild and moderate uncomplicated hypertension.
3. Its long-term side effects had not been studied yet. The effect on pregnancy and lactating mother were not known and further research will be necessary to find out its mode of action, determination of active compounds in modified TMF-28 and its long-term side effect.

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THANK YOU VERY MUCH FOR YOUR ATTENTION

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