



Study of fixed dose combination for the management of cardiovascular diseases

Shaik Nazeera, D.R. Brahma Reddy

Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalle, Guntur, Andhra Pradesh, India

Received: 26-11-2018 / Revised Accepted: 31-12-2018 / Published: 01-01-2019

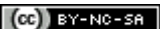
ABSTRACT

An Epidemic of Cardiovascular disease(CVD) is a predicted in the Indian subcontinent as a result of change in demographics and lifestyle and poor childhood nutrition impacting on disease in adult life. Lack of facilities for diagnosis and treatment of CVD and the cost of treatment mean that large sections of the Indian populations have poor access to both prevention and treatment. One cost effective approach, which could achieve substantial benefits within a few years, is provision of combined Cardiovascular(CV) medication to those at highest risk. The study was multicentre prospective open labeled single armed 12 week study. This includes Adults Male or Female age 18-75 years. Patients with at least one risk factor for cardiovascular disease namely Hypertension $\geq 139/89$ mm of Hg and $\leq 180/110$ mm of Hg according to JNC-VII guidelines and lipid profile LDL-C ≥ 130 mg/dl or LDL-C > 100 mg/ dl with CAD Equivalents or patient with coronary artery disease or high cardiovascular risk factors. At the screening visits. the total number of patients successfully completed the study were 27 as per inclusion criteria. The safety of combination pill on Moderate & Severe Hypertensive patients laboratory investigations show there is no increase in the SGOT, SGPT, Serum Creatinine, & Serum Electrolyte levels. so the combination pill consider as safe. The combination pill show higher safety.

Keywords: Multicentre, Open labeled, Risk factor, Cardiovascular disease

Address for Correspondence: Shaik Nazeera, D.R. Brahma Reddy, Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenappally, Guntur, Andhra Pradesh, India; E-mail: shaiknazeera73@gmail.com

How to Cite this Article: Shaik Nazeera, D.R. Brahma Reddy. Study of fixed dose combination for the management of cardiovascular diseases. World J Pharm Sci 2019; 7(1): 16-28.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License, which allows adapt, share and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms. 

INTRODUCTION

An epidemic of Cardiovascular disease (CVD) is a predicted in the Indian subcontinent as a result of change in demographics and lifestyle and poor childhood nutrition impacting on disease in adult life. In contrast to the west the prevalence of ischemic heart disease in India has been steadily increasing over the last two decades, from around 1-4% to over 10%, these figures are based on survey data but supported by clinical impression the prevalence in rural areas is about half that of urban populations. It is predicted that CVD will be the leading cause of death in India by 2010.

Asian Indians have higher prevalence of premature ischemic heart disease than Europeans, Chinese, and Malayas, this is likely to be influenced by conventional risk factors such as smoking, blood pressure and cholesterol levels plus an increasing prevalence of insulin resistance and other metabolic abnormalities.

Reducing CVD and the impact of the epidemic will require extensive public health strategies at the population and individual levels. The lack of facilities for diagnosis and treatment of CVD and the cost of treatment mean that large sections of the Indian populations have poor access to both prevention and treatment. One cost effective approach, which could achieve substantial benefits within a few years, is provision of combined Cardiovascular (CV) medication to those at highest risk.

Indications for three classes of treatment (antiplatelet therapy, blood pressure lowering and cholesterol lowering) exist among people at highest risk of CVD. Individuals with symptomatic coronary or cerebrovascular disease or diabetes with complications have over a 20% risk of a CV event in the next 5 years.

METHODOLOGY

Study design and setting: The study was multicentre prospective open labeled single armed 12 week study.

Ethical considerations: The ethical committee will be provided with the reports of the trial progress and will be promptly receive all adverse events reports.

Inclusion criteria:

- Adults Male or Female age 18-75 years.
- Patients with at least one risk factor for cardiovascular disease namely hypertension \geq 139/89 mmHg and \leq 180/110 mm of Hg according to JNC-VII guidelines and lipid profile LDL-C \geq 130mg/dl or LDL-C $>$ 100 mg/dl with CAD Equivalents or patient with coronary artery disease or high cardiovascular risk factors. At the screening visits.

RESULTS

The total numbers of patients enrolled were 30 as per the inclusion criteria of the study. All the patients were found to be complaint as per the study protocol except for three subjects, they were withdrawn from the study (patient NO.3 and 21) due to his absence from visits 2,3,4 and One patient (patient no 30) was withdrawn from the study due to the adverse event. The total number of patients successfully completed the study were 27 as per the inclusion and exclusion criteria.

The total 27 patients were divided in to 2 groups Moderate (Systolic BP 139-159) and Severe(Systolic Bp $>$ 159) hypertensive patients according to their blood pressure levels. Out of 30 patients 23 patients are under Moderate Hypertensive and 4 No of patients under severe hypertensive patients.

Visit 1 Moderate and Severe hypertensive patients systolic and diastolic, LDL-C, Triglyceroids, Total cholesterol and HDL levels are compared with mean of visit 2,3,4. These comparisons are represented in the figure.

DISCUSSION

The efficacy of combination pill on Moderate Systolic Hypertensive patients was shown that $P < 0.05$ ($P = 0.003$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the Systolic Blood Pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Moderate Diastolic Hypertensive patients was shown that $P < 0.05$ ($P = 0.001$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the Diastolic Blood Pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients Total Cholesterol Levels in patients was shown that $P < 0.05$ ($P = 0.001$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the Cholesterol higher level and doesn't shown any side effects during the 4 visits

The efficacy of combination pill on Moderate Hypertensive patients LDL-C Levels in patients was shown that $P < 0.05$ ($P = 0.001$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the LDL-C higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients Triglyceride Levels in patients was shown that $P < 0.05$ ($P = 0.004$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the Triglyceride Levels higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Moderate Hypertensive patients HDL Level in patients was shown that $P < 0.05$ ($P = 0.005$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has increased the HDL Levels higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Severe Systolic Hypertensive patients was shown that $P < 0.05$ ($P = 0.001$). the combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the Systolic Blood pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Severe Diastolic Hypertensive patients was shown that $P < 0.05$ ($P = 0.003$). The combination pill was consider as effective. so the combination pill show higher efficacy the drug has decreased the diastolic blood pressure higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on severe hypertensive Cholesterol levels in patients was shown that $P < 0.05$ ($P = 0.004$). the combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the cholesterol higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on severe hypertensive LDL-C levels in patients was shown that $P < 0.05$ ($P = 0.005$). the combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the LDL-C higher levels and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on severe hypertensive triglyceride levels in patients was shown that $P < 0.05$ ($P = 0.001$). The combination pill was consider as effective. So the combination pill show higher efficacy the drug has decreased the triglyceride levels higher level and doesn't shown any side effects during the 4 visits.

The efficacy of combination pill on Severe Hypertensive HDL Levels in patients was shown that $P < 0.05$ ($P = 0.003$). The combination pill was consider as effective. So the combination pill show

higher efficacy the drug has increased the HDL Levels higher level and doesn't shown any side effects during the 4 visits.

The safety of combination pill on Moderate and Severe Hypertensive Patients laboratory investigations show there is no increase in the SGOT, SGPT, Serum Creatinine and Serum electrolyte levels so the combination pill was consider as safe. The combination pill show higher safety.

CONCLUSION

The efficacy of Lisinopril and Simvastatin, Aspirin, Hydrochlorothiazide combination was assessed by mean decrease in blood pressure, LDL-C, TG and Total Cholesterol level the therapy also increased HDL Levels after visit 1 (screening) by application of suitable statistical parameters ANOVA. The total numbers of patients enrolled were 30 as per the inclusion and exclusion criteria of the study.

All the patients were found to be complaint as per the study protocol except for three subjects, who was withdrawn from the study (patient No 3 and 21) due to his absence from visits 2, 3, 4 and one patient (patient No 30) was withdrawn from the study due to the adverse event (Severe Dry Cough). the total number of patients successfully completed the study were 27 as per the inclusion and exclusion criteria.

Result of the present study suggest a significant decrease in the all the efficacy parameters ($p < 0.005$) concluding that the drug combination has effective in decreasing the blood pressure and LDL-C levels.

The safety parameters were assessed by concentrating on the adverse drug event during the 4 visits. The laboratory investigation show there is no increase in the SGOT, SGPT, Serum Creatinine and serum electrolytes. No serious and investigational adverse events were reported.

In this study is observed that the fixed dose combination pill showing 100% compliance it can be concluded that the calculating the difference between 28 tablets therapy for 28 days and comparing with number of tablets left in the container.

Therefore, the drug combination Lisinopril (5mg), Simvastatin (10mg) and Aspirin (75mg) and Hydrochlorothiazide (12.5mg) was found to have maximum safety with minimum adverse events reported, which is helpful in treatment of patients with hypertension and Dyslipidemia or coronary artery disease.

Table -1: Moderate Systolic Hypertensive Patients Data

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	1	150	140	140	140	140
2	4	150	140	140	130	136.6
3	7	150	140	130	140	136.6
4	8	140	130	130	120	126.6
5	9	150	140	140	140	140
6	10	150	140	140	140	140
7	11	140	120	120	120	120
8	12	140	120	130	130	126.6
9	14	140	120	120	120	120
10	15	150	140	140	130	136.6
11	16	150	160	150	120	143.3
12	17	140	130	130	130	130
13	18	150	140	160	140	146.6
14	19	150	140	130	150	140
15	20	140	150	150	130	143.3
16	22	140	130	140	150	140
17	23	140	130	130	130	130
18	24	140	140	130	130	133.3
19	25	140	140	120	130	130
20	26	140	140	140	140	140
21	27	150	140	130	140	136.6
22	28	140	140	140	130	136.6
23	29	150	150	150	130	143.3

Figure1: Moderate Systolic Hypertensive Patients Data

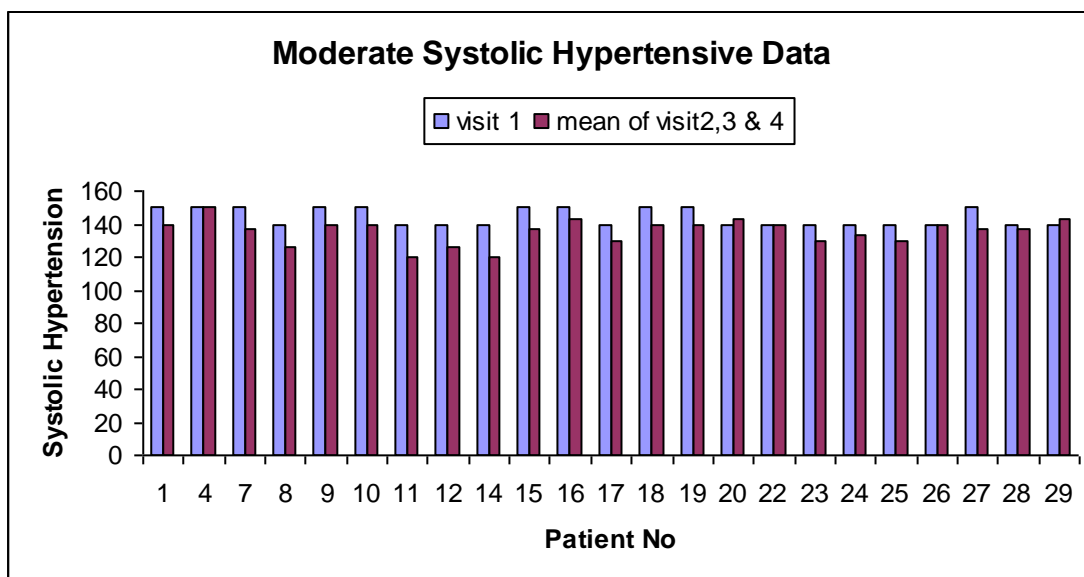


Table – 2: Moderate Diastolic Hypertensive Patients Data

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	1	100	90	80	80	83.3
2	4	100	100	90	100	96.6
3	7	100	100	80	90	90
4	8	90	80	80	80	80
5	9	90	90	90	80	86.6
6	10	90	90	90	90	90

7	11	90	80	80	90	83.3
8	12	100	80	80	80	80
9	14	100	80	80	80	80
10	15	100	100	90	90	93.3
11	16	100	90	90	70	83.3
12	17	100	80	90	80	86.6
13	18	100	100	100	100	100
14	19	100	90	90	90	90
15	20	90	90	90	100	93.3
16	22	100	90	90	90	90
17	23	90	90	80	80	83.3
18	24	100	90	90	90	90
19	25	100	90	80	90	86.6
20	26	100	100	100	100	100
21	27	90	80	90	80	86.6
22	28	100	100	90	90	93.3
23	29	100	90	90	80	86.6

Figure – 2 : Moderate Diastolic Hypertensive Patients Data

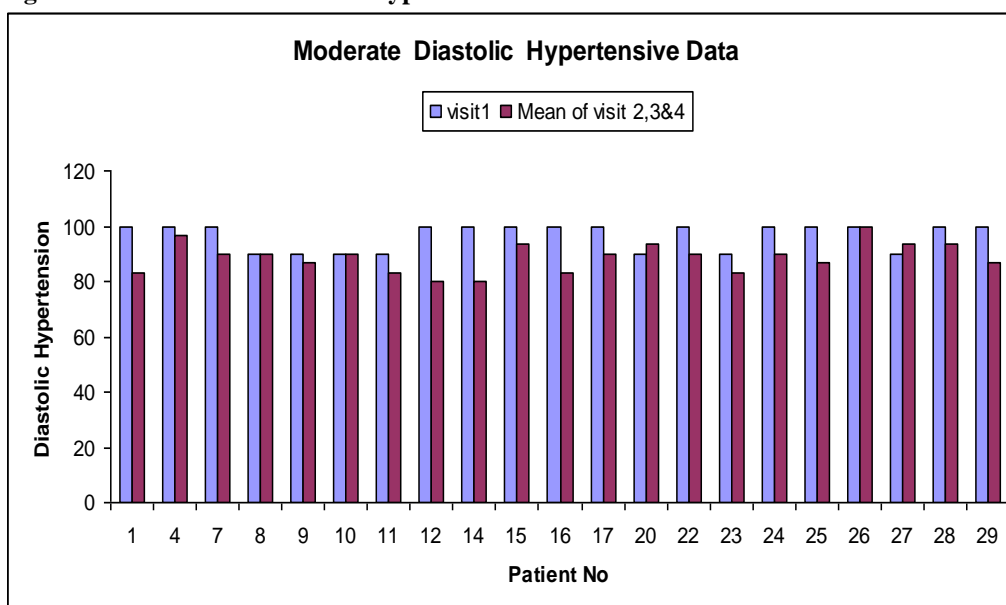


Table – 3: Moderate Hypertensive Patients LDL-C Levels

S.NO	Patient no	visit 1	visit2	visit3	visit4	Mean of visit 2,3&4
1	1	136	98	82	100	93.3
2	4	161	140	130	104	124.6
3	7	133	84	87	96	89
4	8	84	84	101	94	83
5	9	160	101	124	76	100.3
6	10	138	127	53	136	105.3
7	11	139	121	160	121	107.3
8	12	133	105	117	116	112.6
9	14	162	73	66	80	73
10	15	173	57	120	99	92
11	16	186	147	108	125	126.6

12	17	144	120	114	106	113.3
13	18	156	112	104	112	109.3
14	19	141	112	104	112	109.3
15	20	193	84	79	105	89.3
16	22	189	107	122	120	116.3
17	23	186	106	129	132	122.3
18	24	143	65	128	109	100.6
19	25	130	72	162	85	106.3
20	26	148	121	46	78	81.6
21	27	152	67	134	98	99.6
22	28	130	88	140	110	112.6
23	29	147	101	113	88	100.6

Figure – 3: Moderate Hypertensive Patients LDL-C Levels

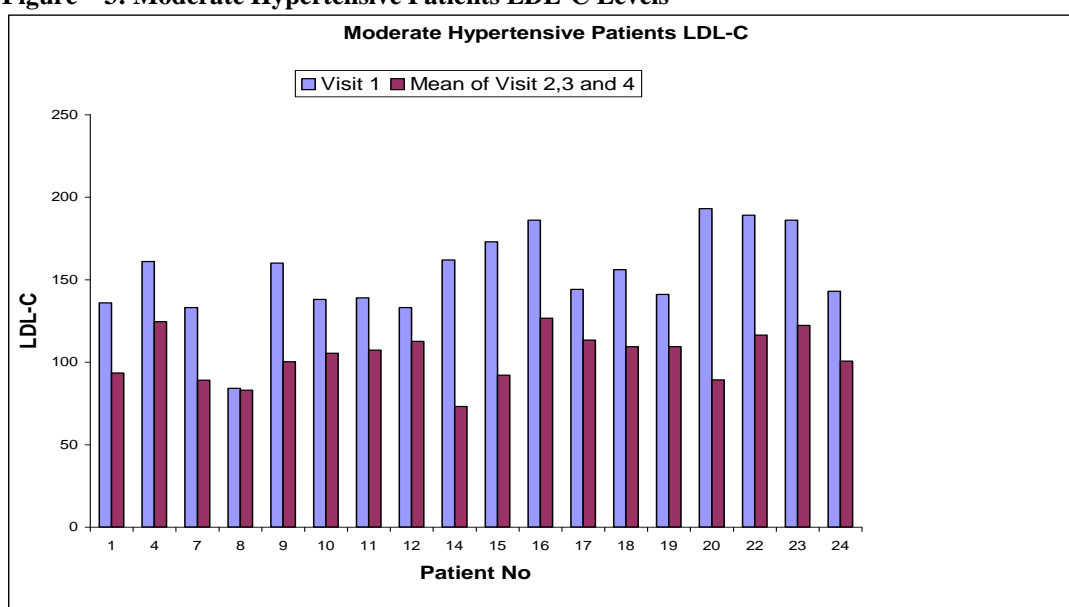


Table – 4: Moderate Hypertensive Patients Triglyceride Levels

S.NO	Patient no	visit 1	visit2	visit3	visit4	Mean of visit 2,3&4
1	1	256	187	220	172	193
2	4	243	173	173	158	168
3	7	208	180	185	167	177.3
4	8	247	220	225	169	204.6
5	9	230	198	180	172	183.3
6	10	225	205	153	143	167
7	11	182	164	156	123	147.6
8	12	142	124	128	118	123.3
9	14	184	162	62	68	97.3
10	15	153	145	138	130	137.6
11	16	317	224	240	243	235.6
12	17	206	185	236	101	174
13	18	167	96	158	133	129
14	19	111	90	94	89	91
15	20	126	105	121	88	104.6
16	22	189	134	140	155	143
17	23	299	109	311	144	188

18	24	152	109	115	116	113.3
19	25	89	80	97	54	77
20	26	140	80	137	133	116.6
21	27	354	132	228	142	167.3
22	28	393	231	217	241	229.6
23	29	199	197	156	121	158

Figure – 4: Moderate Hypertensive Patients Triglyceride Levels

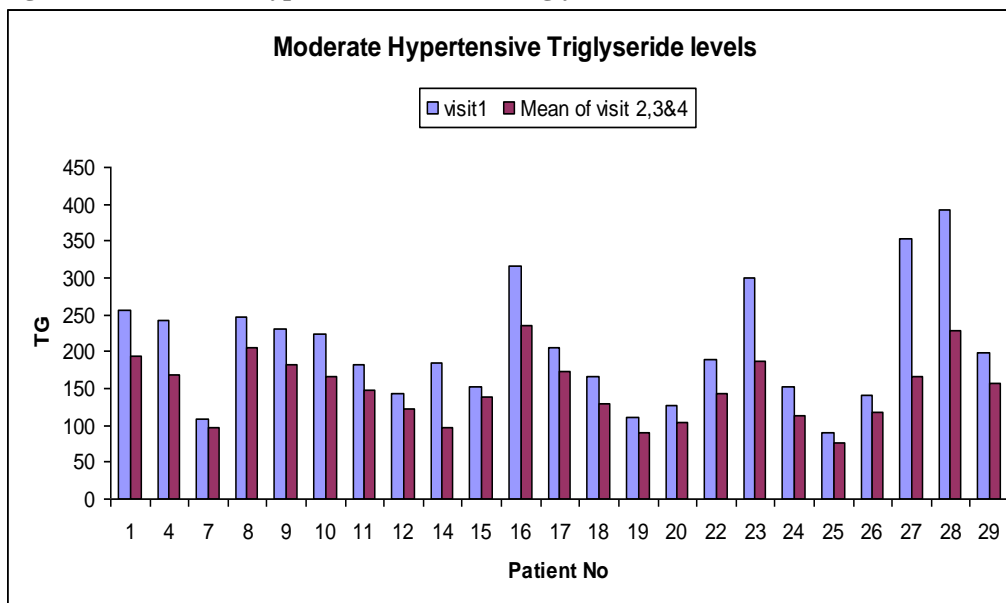


Table – 5: Moderate Hypertensive Patients Total Cholesterol levels

S.NO	Patient no	visit 1	visit2	visit3	visit4	Mean of visit 2,3&4
1	1	213	154	154	172	160
2	4	216	192	187	141	173.3
3	7	195	141	132	148	140.3
4	8	135	135	145	122	134
5	9	230	152	211	172	178.3
6	10	193	171	122	210	167.6
7	11	216	196	235	198	209.6
8	12	190	161	146	167	158
9	14	226	137	112	148	132.3
10	15	227	238	176	181	198.3
11	16	253	209	183	205	199
12	17	177	180	177	160	172.3
13	18	231	183	141	169	164.3
14	19	218	179	182	209	190
15	20	253	138	133	163	144.6
16	22	262	165	195	188	182.6
17	23	255	169	216	196	193.6
18	24	200	118	184	163	155
19	25	186	118	256	142	172
20	26	222	182	146	148	158.6
21	27	258	167	185	148	166.6
22	28	225	207	177	149	177.6
23	29	224	172	177	156	168.3

Figure – 5: Moderate Hypertensive Patients Total Cholesterol levels

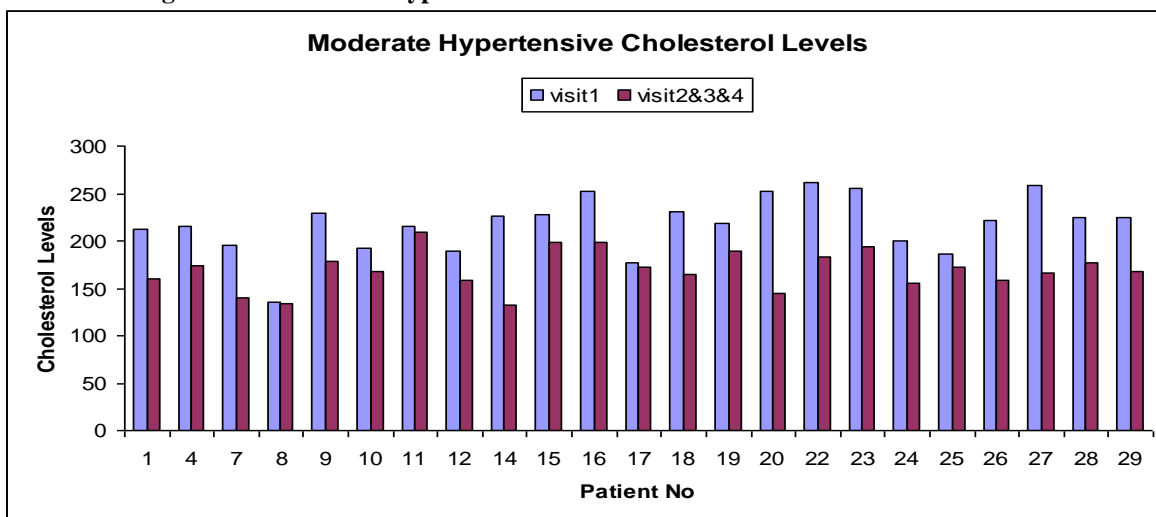


Table – 6: Moderate Hypertensive Patients HDL levels

S.NO	Patient No	visit 1	visit2	visit3	visit4	Mean of visit 2,3&4
1	1	33	36	48	56	46.6
2	4	38	48	52	63	54.3
3	7	40	38	42	56	45.3
4	8	28	28	26	31	28.3
5	9	49	42	65	67	58
6	10	34	43	57	67	55.6
7	11	59	60	67	73	66.6
8	12	31	45	42	56	51
9	14	41	40	42	55	45.6
10	15	33	27	43	56	42
11	16	28	40	45	44	43
12	17	36	40	40	58	46
13	18	55	59	56	62	59
14	19	61	54	74	68	65.3
15	20	42	55	62	64	60.3
16	22	46	38	48	62	49.3
17	23	41	43	42	57	47.3
18	24	35	36	37	42	38.3
19	25	46	43	61	48	50.6
20	26	50	53	56	62	57
21	27	43	46	53	57	52
22	28	29	32	31	31	31.3
23	29	54	53	50	51	51.3

Figure – 6: Moderate Hypertensive Patients HDL levels

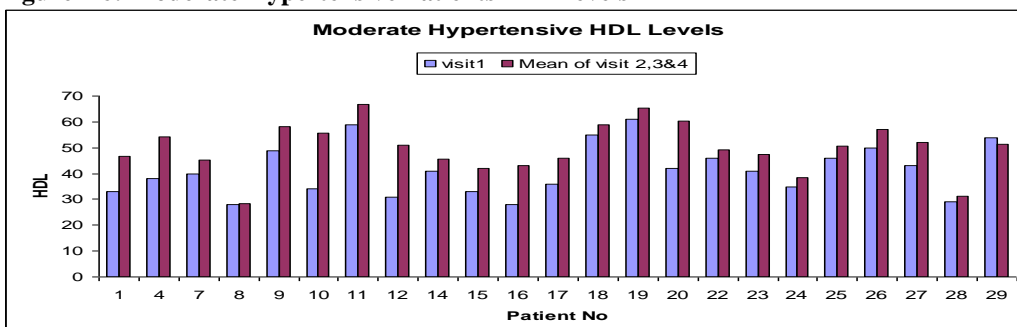


Table – 7: Severe Systolic Hypertensive Patients Data

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	160	150	130	130	136.6
2	5	160	140	120	130	130
3	6	160	150	130	130	136.6
4	13	160	130	160	130	140

Figure – 7: Severe Systolic Hypertensive Patients Data

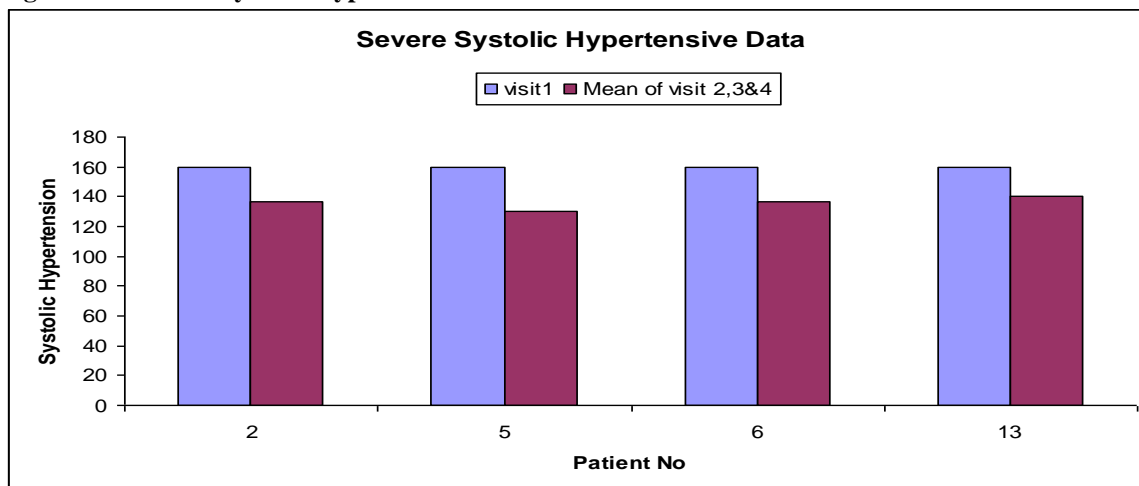


Table – 8: Severe Diastolic Hypertensive Patients Data

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	110	100	90	85	91.6
2	5	100	80	80	90	83.3
3	6	100	90	90	90	90
4	13	110	90	82	76	82.6

Figure – 8: Severe Diastolic Hypertensive Patients Data

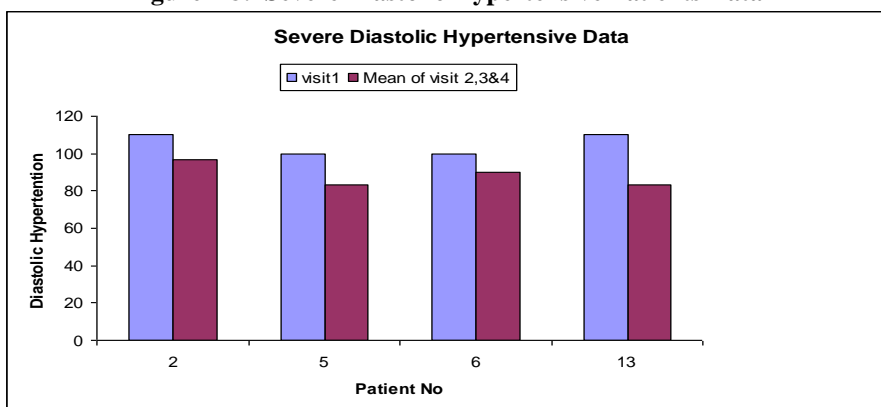


Table – 9: Severe Hypertensive Patients LDL-C Levels

SE.NO	Patient No	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	213	178	206	152	181
2	5	236	184	198	178	186.6
3	6	209	172	153	169	164.6
4	13	228	232	197	156	195

Figure – 9: Severe Hypertensive Patients LDL-C Levels

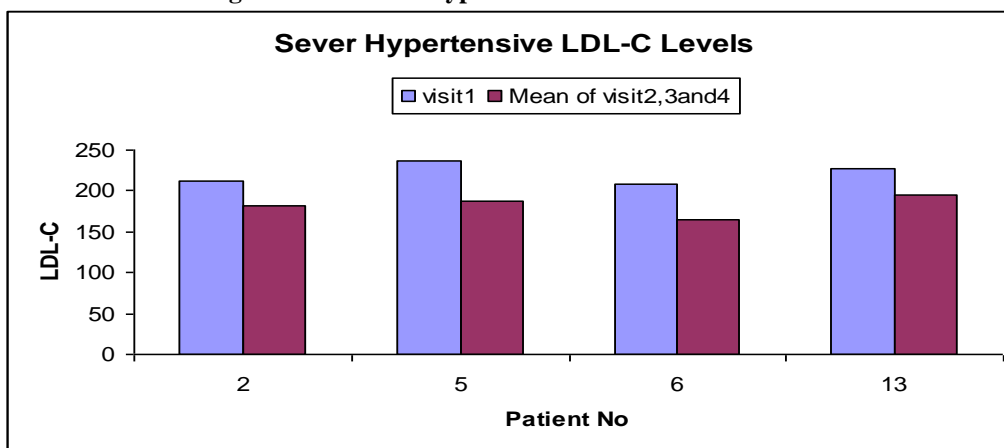


Table – 10: Severe Hypertensive Patients Triglyceride Levels

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	154	67	134	98	99.6
2	5	166	109	125	127	120.3
3	6	147	95	89	75	86.3
4	13	157	98	81	94	91

Figure – 10: Severe Hypertensive Patients Triglyceride Levels

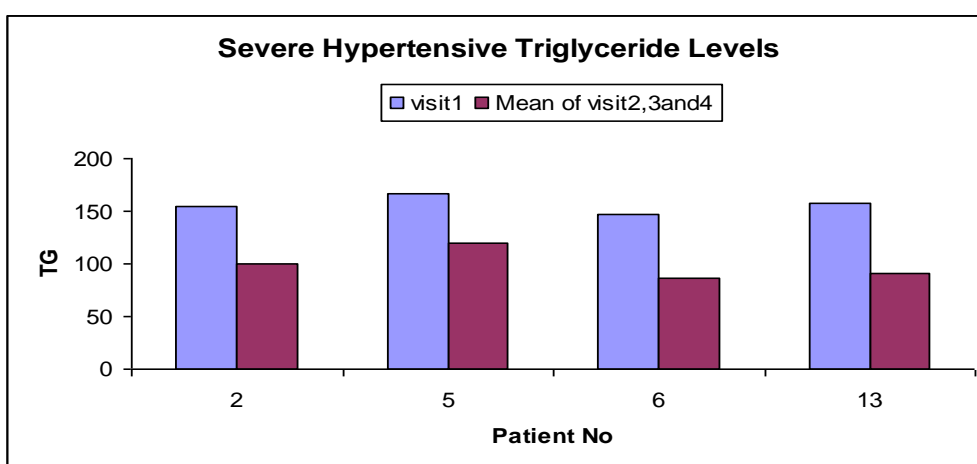


Table – 11: Severe Hypertensive Patients Total Cholesterol Levels

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	223	120	145	147	137.3
2	5	238	171	185	198	184.6
3	6	202	143	136	128	135.6
4	13	204	149	123	145	139

Figure – 11: Severe Hypertensive Patients Total Cholesterol Levels

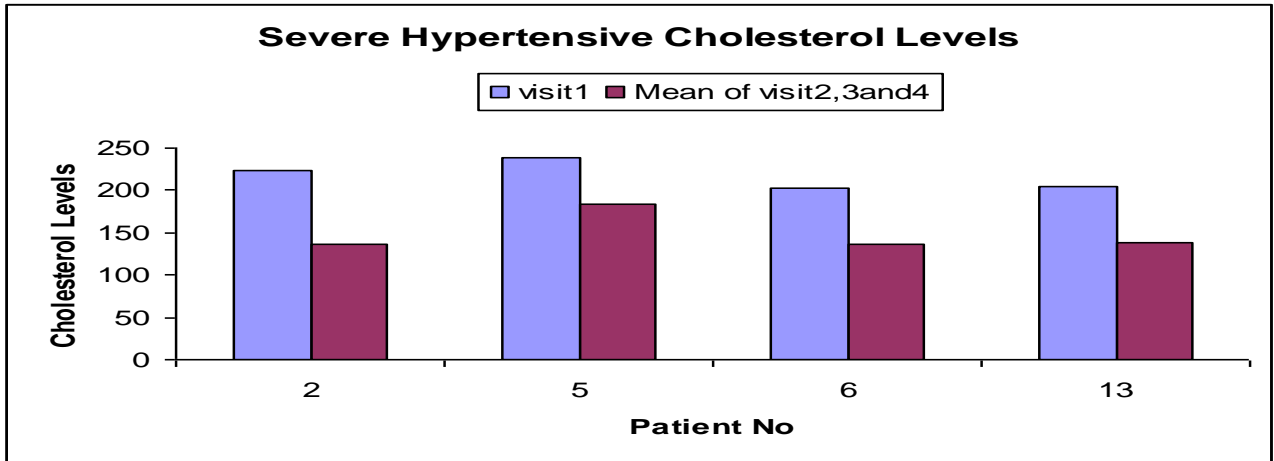


Table – 12: Severe Hypertensive Patients HDL levels

SE.NO	Patient no	visit1	visit2	visit3	visit4	Mean of visit 2,3&4
1	2	43	44	55	52	47
2	5	35	46	45	49	46.6
3	6	36	53	62	67	60.6
4	13	28	32	37	42	37

Figure – 12: Severe Hypertensive Patients HDL levels

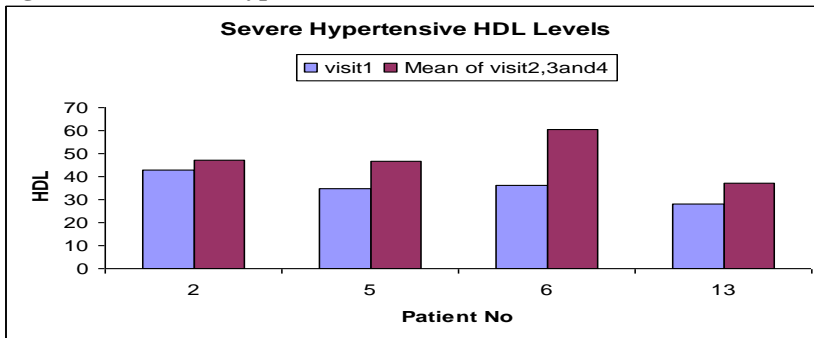


Table-13: Efficacy of Combination Pill on Hypertension

	Systolic Hypertension		Diastolic Hypertension	
	Visit-1	Mean of Visit 2,3,and 4	Visit-1	Mean of Visit 2,3,and 4
Moderate Hypertension (n = 23)	144.78 ± 1.065	137.08 ±2.172**	96.96 ±0.981	88.67 ± 1.235***
Severe Hypertension (n=4)	160.0 ±0.00	135.8 ±2.09***	105.0 ± 2.88	86.87 ± 2.29**

n values are given as mean ± SEM; **, *** Values are statistically significant compared to Visit 1(Base line) at P<0.01, P<0.001 respectively

Table – 14: Efficacy of Combination Pill on Hyperlipidemia

	LDL-C		Triglycerides		Total Cholesterol		HDL	
	Visit-1	Mean of Visit 2,3and4	Visit-1	Mean of Visit 2,3and4	Visit-1	Mean of Visit 2,3and4	Visit-1	Mean of Visit 2,3and4
Moderate Hypertensive (n=23)	150.60±5.119	102.96±2.936***	209.21±16.047	153.30±8.95**	217.60±6.25	169.4±4.30***	41.39±2.04	49.73±1.99**
Severe Hypertensive (n=4)	221.5±6.33	181.8±6.414**	156.0±3.93	99.3±7.52***	216.75±8.51	149.12±11.8**	35.50±3.06	57.9±3.64**

n values are given as mean ±SEM

, * Values are statistically significant compared to Visit 1(Base line) at P<0.01, P<0.001 respectively

BIBLIOGRAPHY

- [1] Reddy K. Primordial prevention of coronary heart disease in India: challenges and opportunities. *Preventive Medicine* 1999;29(6 pt 2):s119-23.
- [2] Reddy K. Cardiovascular disease in India. *World health statistics quarterly* 1993;46(2): 101-7.
- [3] Padmavathi S. Prevention of heart disease in India in the 21st Century; Need for a concerted effort. *Indian heart journal* 2002;54:103.
- [4] Krishnaswamy S. Prevalence of coronary artery disease in India. *Indian heart journal* 2002;54:103.
- [5] Mohan V, Deepa R, Rani S, Premalatha G. Prevalence of coronary artery disease and its relationship to lipids in a selected population in south India. *Journal of the American college of cardiology* 2001;38:682-687.
- [6] Bahl V, Prabakaran D, Karthikeyan G. Coronary artery disease in Indians, *Indian heart journal* 2001;53(6):707-13.
- [7] Reddy K Kumar D, Rayudu N, Sastry B, Raju B. Prevalence of coronary heart disease and risk factors in an urban Indian population : Jaipur heart watch-2. *Indian heart journal* 2002;54:697-701.
- [8] Gupta R, Gupta V, Sarma M, Bhatnagar S, Thanvi J, Sharma V, Prevalence of coronary heart disease and risk factors in an urban Indian population; Jaipur heart watch-2. *Indian heart Journal* 2002;54:59-66.
- [9] New Zealand Guidelines Group. Best practice evidence-based guidelines. The assessment and management of cardiovascular risk. Consultation draft. August 2003 Ed: New Zealand Guidelines Group, 2003.