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Research Article

EVALUATION OF COMPLIANCE AND BLOOD PRESSURE REDUCTION IN PATIENTS TREATED WITH AMLODIPINE AND METOPROLOL SINGLE PILL COMBINATION VS. ITS INDIVIDUAL COMPONENTS

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ABSTRACT

The objective of study is to compare the efficacy of single pill combination containing Metoprolol and Amlodipine (Metoprolol/Amlodipine 25/2.5) to its individual components in patients having hypertension in Gujarat region. We conducted this study at multicentre and this was open-label, and prospective in patient with Hypertension (140-180 mmHg/90-114 mmHg) in 3 centers from one city. Patients having hypertension were treated with one of three treatments (Metoprolol/Amlodipine 25/2.5, Amlodipine 5mg, Metoprolol 50mg) and treated for 12 weeks with three follow up visits to record BP and clinical status. At baseline, treatment groups were balanced; mean (standard deviation, SD) sitting BP was 159.7 (±5.35)/102.4 (±3.85) mmHg. The greatest reduction in BP from baseline to 12 weeks was seen in the SPC group (14.46/10.08mmHg; $p<0.05$). The remaining group demonstrated a significant decline from baseline ($p<0.05$): Amlodipine 5, -11.66/-8.72; Metoprolol 50, -9.18/-7.46. Reduction in BP by SPC however was not statistically superior to monotherapies. Responder rates (sitting DBP<90 mmHg or reduction >/=10 mmHg) were 92 % in SPC group. There were no reports of SAEs related to study medications. There were not any discontinuations reported in three groups due to adverse events. Blood pressure reduction from combining drugs from two different classes can be predicted on the basis of additive effects. SPC of Metoprolol and Amlodipine (25/2.5) is more effective as comparison with doubling dose of single individual drug in achieving target BP levels in patients with mild to moderate hypertension.

Keywords: Amlodipine, Metoprolol, hypertension, single pill combination

INTRODUCTION

Hypertension is today's silent killer. It affects 10-20% of world population. Hypertension is a major risk factor for cardiovascular and renal diseases. Untreated hypertension can reduce life expectancy by approximately 5 years. Despite the importance of treating high blood pressure to reduce cardiovascular complications, most patients do not achieve the target blood pressure (BP). The seventh Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7) recommends appropriate treatment of hypertension and the need for combination therapy to achieve and maintain the goal BP. The combination of

antihypertensive therapy by reporting that irrespective of the initial antihypertensive agents, more than 40% of hypertensive patients require 2 or more drugs at the end of four years of treatment.

Calcium channel blockers inhibit the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Beta-blockers suppress renin release from kidney, reduces noradrenaline release from sympathetic terminals and with continued treatment, resistance vessels gradually adapt to chronically lower cardiac output that decreases total peripheral resistance. JNC 7 has recommended both of these drug classes as first line therapy for treating hypertension.

Amlodipine is a long acting calcium channel blocker with an elimination half-life of 35-50 hrs. The long half-life makes it an ideal choice for once a day dosing (in a fixed-dose combination). Metoprolol is the prototype of beta-1 cardio selective blockers.

FDC of calcium channel blockers and β-blockers have complementary antihypertensive effects with low rates of adverse effects which observed in randomized controlled trials. The availability of two drug combination in a FDC reduces the pill burden and may improve treatment adherence in a chronic disease like hypertension.

There are no published studies to-date with a combination of metoprolol and amlodipine in hypertension. We conducted a open labeled, multicentre study to compare the efficacy and safety of Single pill combinations of amlodipine and metoprolol with its individual components in Indian patients especially region of Gujarat with hypertension.

The primary objective was to demonstrate that the SPC of metoprolol 25 mg and amlodipine 2.5mg was superior to monotherapy with its individual components, metoprolol 50mg and amlodipine 5mg in reducing BP. The secondary objectives were, to, a) assess the number of responders (percent of patients with sitting DBP <90mmHg or a reduction of sitting DBP >/=10mmHg) b) assess the compliance with treatment medications.

Methods

The study protocol was approved by independent ethics committee. Written informed consent was obtained from all patients prior to enrolment in the study.

Patients

Eligible patients were 18-75 years of age with a SBP ≥140 mmHg and DBP ≥90 mmHg, documented during two hospital visits. We excluded patients with recent stroke, heart attack, or heart surgery in last 3 months, diagnosis of hyperthyroidism. We also excluded patients with resting heart <55bpm, patients had atrioventricular block, dyspnea class III/IV or had history of allergy or hypersensitivity to study medication.

Study design

This study was observational study, multicentric, open label conducted in 2 centres of Gujarat in one city between December 2010 to April 2011. Total five visits were required for each subject over a treatment period. At the first visit, eligibility assessment, informed consent, and necessary investigations were carried out to screen the patient for hypertension. All patients underwent a clinical examination and recording of heart rate, and BP. We measured SBP and DBP of patients included in the study at all sites using a digital automatic blood pressure monitor (Omron, model HEM-7080, Omron health care Co., Ltd. Kyoto, Japan). Laboratory measurements included clinical chemistry (lipid profile, serum electrolytes, serum creatinine).

If already on an antihypertensive medication, the patient underwent a washout period of at least 1 week before enrollment. At the end of the washout period, all patients were re-assessed for eligibility. Fig 1.

Efficacy assessment

The primary efficacy outcomes were the changes in sitting SBP and DBP between SPC of metoprolol 25mg and amlodipine 2.5mg and its individual components (metoprolol 50mg and amlodipine 5mg) from visit 2 (week 0). The secondary objective was responder rate (responders were patients with sitting DBP <90 mmHg or reduction in sitting DBP >/=10 mmHg [9]) and assessed compliance with treatment medication. BP was measured at all visits by the study physician. BP and heart rate were measured after a rest for 5 minutes. At least three sitting BP measurements, at an interval of 2 minutes were recorded. The BP recorded for assessment was the mean of the three consecutive readings taken with the patient sitting down.

Compliance assessment

The compliance was carried out by residual tablet counting. Residual tablet counting means that tablet counts may be performed on a regular basis and comparative number of used tablets over a period can be noted down.

Sample size

A total sample size was 150 patients with 50 patients in each arm.

Statistical analysis

Data were described using mean and SD when normally distributed. The primary statistical analysis was a one-way analysis of variance (ANOVA) of change in BP with the baseline SBP or DBP. The three treatment groups considered in this analysis were metoprolol 25 mg + amlodipine 2.5 mg, amlodipine 5 mg, metoprolol 50 mg. We used the paired student 't' test to analyze change in BP from baseline to the end of study.

Results

Patient allocation and baseline characteristics

Out of 150 patients 50 patients treated with Metoprolol 25mg+ amlodipine 2.5mg, 50 patients were treated with Metoprolol 50mg and rest 50 were treated with Amlodipine 5mg. Details of patient disposition are presented in Figure 2. Out of 150 patients no one discontinued from the study. Baseline characteristic were comparable among the three treatment groups (table 1). The mean age was 56.96(± 8.96) years.

Treatment efficacy

Systolic BP (SBP) and Sitting Diastolic BP (DBP)

At 12 weeks, there was a significant reduction in BP from baseline in all 3 treatment groups in populations (all $p< 0.05$). The maximum reduction was seen in the SPC group (Metoprolol 25mg+amlodipine 2.5mg) of 14.5 (±2.53) mmHg SBP and 10.1(±1.79) mmHg DBP. (Table 4). Furthermore, the SPC group showed the most rapid and greatest reduction in both SBP and DBP compared to monotherapy groups. (Fig.3 [A and B]). The reduction in BP across the three different groups were not statistically different. The reduction in BP by the SPC was not statistically superior to monotherapies. (Table 5).

Responder rates

More patients on SPC therapy (92%) responded (sitting DBP <90 mmHg or a reduction of sitting DBP>/=10 mmHg) compared to monotherapies with Metoprolol 50 (22%) and Amlodipine 5 (50%). (Table 7).

Safety

The most common adverse effects (AEs) overall were headache (12%), peripheral edema (12%), fatigue (10%) and dizziness (6%). Table 8. Metoprolol caused maximum reduction in heart rate 8.5 (± 2.62) bpm and least reduction was seen in the Amlodipine 5 mg group 0.4 (±1.16). Table 6. None of the patients' SBP fell below 90 mmHg and DBP below 60 mmHg. None of the patients experienced SAEs during the study.

DISCUSSION

This is the multicentre trial to assess the efficacy and safety of dose of SPCs of amlodipine and metoprolol in hypertension. Treatment with these SPCs produced robust reductions in SBP and DBP (-14.5 /- 10.1) in patients with mild to moderate hypertension. A substantial decrease in cardiovascular complications can be achieved even with small reductions in BP. A 2 mmHg reduction in DBP is estimated to decrease the risk of coronary artery disease by 6% and stroke by 15%.

Analyses of pooled results of 3 double blind, placebo controlled studies of metoprolol CR/XL 50 mg once daily demonstrated a reduction of 8.4/4.8 mmHg in supine BP. In direct comparison studies felodipine/Metoprolol 5/50 mg reduces BP more effectively than Amlodipine 5 mg alone as assessed by 24-hour ABPM. In comparison of Metoprolol XL/Amlodipine 25/2.5 mg FDCs was found to be more effective than Losartan plus Amlodipine in the treatment of essential hypertension.

The antihypertensive effect of the combination of felodipine and metoprolol occurs mostly in the first month of treatment with small additional decrease in BP in the second and third months and thereafter little additional decrease. In this study too we observed a similar pattern.

In our study, after 12 weeks of treatment, greater proportion of patients on combination therapies (92% of patients) responded compared to monotherapy with metoprolol or Amlodipine but Long term studies with a

larger sample size may provide some insights and large sample data provide better evaluation of control rate and responder rate with treatment. The study by Dahlof with felodipine/metoprolol combination for 12 weeks, reported a responder rate of 90% and a control rate of 71%. A similar study by Hoffmann in 182 patients, over 12 weeks reported a BP reduction of 28/17mmHg, with 98% responder rate and 73% control rate.

In our study single pill combination of amlodipine and metoprolol were well tolerated with low rates of adverse events (7 events). Overall, headache and peripheral edema were the most commonly reported adverse effects (AEs) as seen in a previous study. Types of AEs reported in our study were similar to those noted in previous studies with felodipine/ metoprolol combinations. No drug related SAEs were reported in SPCs as well as in any of the other treatment groups.

Overall, out of 150 patients no one discontinued from the study. In this study all patients reported more than 80% compliance. Simplified, dosage regimens improve patient compliance especially when the dosage frequency is once daily.

This study is the first multicenteric trial in Indian patients specialy Gujarat region demonstrated that SPCs of amlodipine and metoprolol are safe and effective BP lowering in hypertension. SPCs demonstrated clinically meaningful BP reductions and better responder rates compared to monotherapies. Overall, as well as AE related were lower than reported in previous studies. The rates of hypotension were low and there were no reports of drug related SAEs. Therefore when a combination of metoprolol and amlodipine is indicated, these data provide an evidence-based option that is safe and effective.

Table 1: Baseline Characteristics of Study Participants (N=150)

Characteristics	SPC	Amlo 5	Meto 50
Age	56.8 ± 9.24	57.1 ± 9.15	57.0 ± 8.66
Male	37 (74%)	33 (66%)	30 (60%)
Female	13 (26%)	17 (34%)	20 (40%)
Smoking	19 (38%)	21 (42%)	25 (50%)
IHD	10 (20%)	10 (20%)	10 (20%)
Past PTCA or CABG	14 (28%)	6 (12%)	6 (12%)
MI	15 (30%)	6 (12%)	20 (40%)
DM	25 (50%)	17 (34%)	24 (48%)
Pulse (beats/min)	81.8 ± 8.58	82.2 ± 8.48	80.9 ± 9.49
Sitting SBP mmHg	159.34 ± 5.65	159.02 ± 5.55	159.52 ± 5.69
Sitting DBP mmHg	102.12 ± 4.17	101.98 ± 4.01	101.92 ± 4.02

Table 2: Laboratory Data at Baseline

	SPC group n=50;mean±SD	Amlodipine 5 n=50;mean±SD	Metoprolol 50 n=50; mean±SD
S. Creatinine	1.1 (0.26)	1.1 (0.30)	1.1 (0.28)
K^+	4.2 (0.51)	4.2 (0.49)	4.2 (0.51)
Na^+	137.3 (4.29)	137.5 (4.45)	137.2 (4.59)
HDL	45.7 (9.49)	45.9 (9.72)	45.6 (9.36)
LDL	152.8 (23.67)	152.4 (23.36)	152.9 (24.30)
TG	192.8 (35.77)	193 (35.72)	192.6 (35.29)
Total Lipids	897.1 (89.01)	897.6 (89.15)	895.0 (82.93)
RBS	108.4 (29.55)	114.6 (36.00)	100.3 (11.38)

K^+: Potassium; Na^+: Sodium; HDL: High Density Lipoprotein;
LDL: Low density Lipoprotein; TG: triglyceride; RBS: random blood sugar

Table 3: Mean Changes of Blood Pressure with Treatment

Parameters	Treatment	Baseline	Week 12	p value
DBP	SPC group	102.1 (4.17)	92.0 (3.80)	<0.0001
	Amlodipine	102.0 (4.01)	93.4 (3.63)	<0.0001
	Metoprolol	101.9 (4.02)	94.7 (3.19)	<0.0001
SBP	SPC group	159.3 (5.65)	144.9 (5.91)	<0.0001
	Amlodipine	159.0 (5.55)	147.6 (5.03)	<0.0001
	Metoprolol	159.5 (5.69)	150.5 (4.90)	<0.0001

Table 4: Mean reduction in Blood Pressure with Treatment

Parameters	Treatment	Week 4	Week 8	Week 12
DBP	SPC group n=50; mean±SD	7.0 ± 1.23	8.7 ± 1.54	10.1 ± 1.79
	Amlodipine 5 n=50; mean±SD	6.1 ± 2.54	7.3 ± 2.67	8.6 ± 2.76
	Metoprolol 50 n=50; mean±SD	4.7 ± 1.91	6.2 ± 1.99	7.3 ± 2.05
SBP	SPC group n=50; mean±SD	9.6 ± 1.95	12.3 ± 2.27	14.5 ± 2.53
	Amlodipine 5 n=50; mean±SD	6.8 ± 1.94	9.2 ±1.67	11.5 ± 2.44
	Metoprolol 50 n=50; mean±SD	6.0 ± 2.39	7.6 ± 2.46	9.1 ± 2.76

Table 5: Change in DBP and SBP from Baseline to Week 12 with Treatment

Parameters	Treatment Groups	Change from Baseline to Week 12	
		Confidence Interval	p Value
DBP	SPC vs Amlo5	-2.439 to -0.2808	< 0.05 **
	SPC vs Meto50	-3.699 to -1.541	< 0.05 ***
	Meto50 vs Amlo5	-2.339 to -0.1808	< 0.05 *
SBP	SPC vs Amlo5	-3.924 to -1.676	< 0.05 ***
	SPC vs Meto50	-6.404 to -4.156	< 0.05 ***
	Meto50 vs Amlo5	-3.604 to -1.356	< 0.05 ***

,**, clinical summary of p value**

Table 6: Change in Pulse with Treatment as Per Visit Schedule

Visit	SPC group n=50, mean±SD	Amlodipine 5 n=50, mean±SD	Metoprolol 50 n=50, mean±SD
Visit 1 (week 4)	-4.3 ± 1.78	-0.3 ± 1.17	-7.1 ± 2.15
Visit 2 (week 8)	-6.3 ± 2.64	-0.0 ± 0.43	-8.5 ± 2.62
Visit 3 (week 12)	-6.7 ± 2.86	-0.4 ± 1.16	-8.5 ± 2.62

Table 7: Responder Rates with Treatment

Parameter	SPC Group n=50	Amlodipine 5 n=50	Metoprolol 50 n=50
Responder rate n (%)	46 (92)	25 (50)	11 (22)

Table 8: Rates of Adverse Event in Different Treatment Group

Adverse event	SPC group n (%)	Amlodipine 5 n (%)	Metoprolol 50 n (%)	Total N (%)
Headache	1 (2)	4 (8)	1 (2)	6 (12)
Peripheral edema	2 (4)	3(6)	1(2)	6(12)
Dizziness	2(4)	1(2)	0(0)	3(6)
Fatigue	2(4)	1(2)	2(4)	5(10)

Table 9: Treatment Compliance

	Statistic	SPC group n(%)	Amlodipine 5 n(%)	Metoprolol 50 n(%)
Overall compliance (%)		92.1 ± 2.49	92.7 ± 2.23	92.1 ± 2.49
Visit 1	>60 - <100	44 (88)	50 (100)	44 (88)
	100	6 (12)	0	6 (12)
Visit 2	>60 - <100	50 (100)	50 (100)	50 (100)
	100	0	0	0
Visit 3	>60 - <100	50 (100)	50 (100)	50 (100)
	100	0	0	0

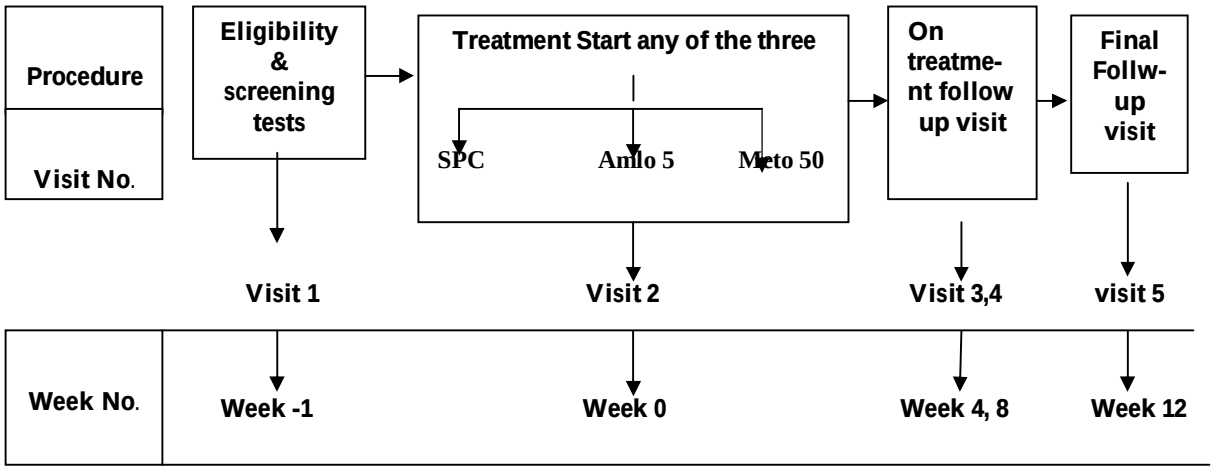


Fig. 1: Study Design

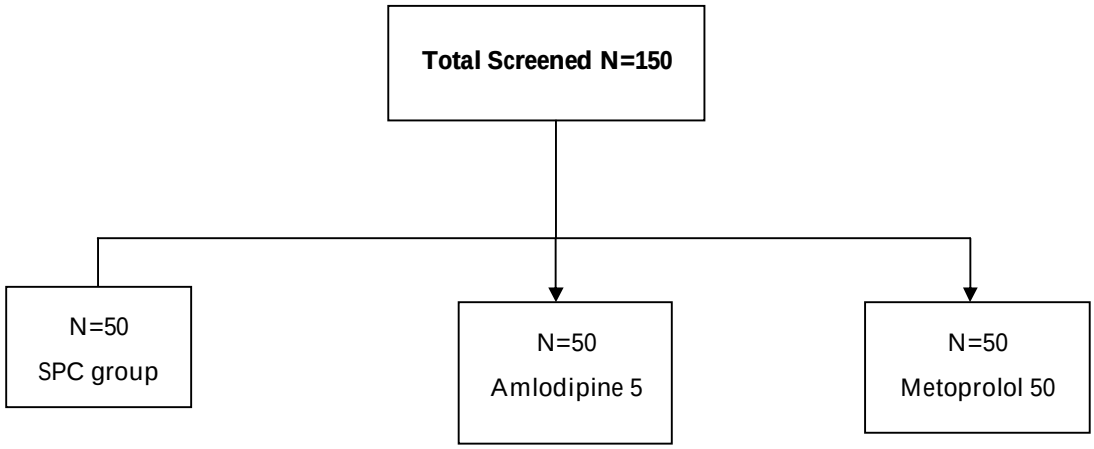
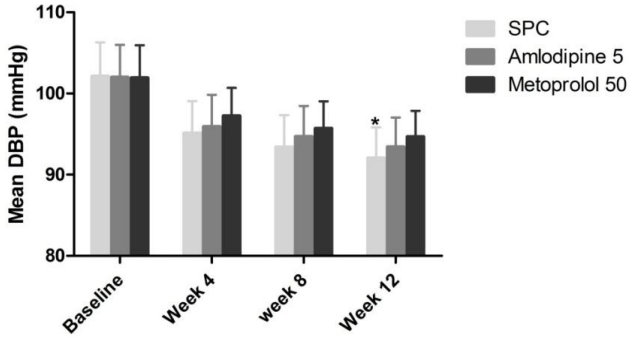
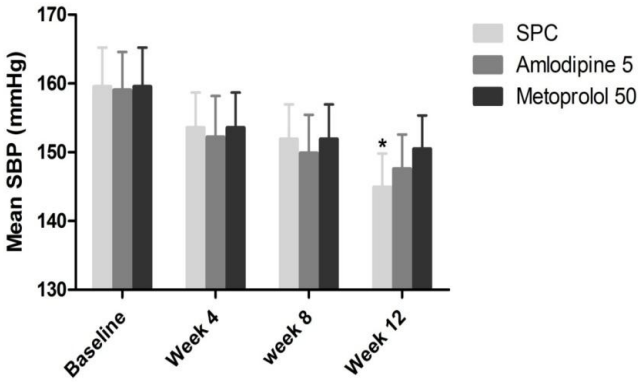


Fig. 2: Allocation of Participants



* Indicated more reduction in DBP as compared to other group

Fig. 3A: Mean DBP Changes with Treatment



*Indicate more SBP reduction as compared to other groups

Fig. 3 B: Mean SBP Changes with Treatment

CONCLUSION

Combination therapy is recommended by treatment guidelines and has become widely accepted by health care providers for the therapy of hypertension. Single pill combinations provide effective antihypertensive treatment by achieving BP goals more frequently, improving patient adherence, and decreasing adverse effects. Blood pressure reduction from combining drugs from two different classes can be predicted on the basis of additive effects. The study shows that SPCs of Metoprolol and Amlodipine (25/2.5) is more effective as comparison with doubling dose of single individual drug in achieving target BP levels in patients with mild to moderate hypertension. Responder rate was high in SPCs group as compared to monotherapy.

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