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Carvedilol As A Treatment Modality In Type-2 Diabetes Mellitus And Hypertension

[1]Dr. Krishnakant Bhatt, Additional professor and Head of Department of Medicine, Government medical college, Surat, Gujarat, India

[2]Dr. Jayesh Ambaliya, [2]Senior resident, Department of Medicine, Government Medical College, Surat, Gujarat

[3]Dr. Piyanka Mody , Assistant professor, Department of Medicine, Government Medical College, Surat, Gujarat

[4]Dr. Siddhant agrawal, 2nd year resident, Department of Medicine, Government Medical College, Surat, Gujarat

[5]Dr. Kalpesh Gohel, 2nd year resident, Department of Medicine, Government Medical College, Surat, Gujarat

[6]Dr. Priyanka Patel, 3rd year resident, Department of Medicine, Government Medical College, Surat, Gujarat

[7]Dr. Dilip Waghela, 3rd year resident, Department of Medicine, Government Medical College, Surat, Gujarat

[8]Dr. Kuldeep Shrimani, 3rd year resident, Department of Medicine, Government Medical College, Surat, Gujarat

[9]Dr. Mansi Parker, 1st year resident, Department of Medicine, Government Medical College, Surat, Gujarat

Corresponding Author: Dr. Piyanka Mody , Assistant professor, Department of Medicine, Government Medical College, Surat, Gujarat

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Abstract

Background: Diabetes Mellitus and Hypertension are a major public health issue and are important modifiable risk factors for premature cardiovascular diseases, estimated to affect 425 million and 1.8 billion individuals worldwide, respectively. The antihypertensive drug Carvedilol, a combined nonselective beta and alpha-1 adrenergic antagonist, has been found to have certain advantages in patients with diabetes, unlike other beta blockers.

Methods:100 patients with Diabetes Mellitus type 2 and hypertension, willing to give consent were included in the study. These were divided into 2 groups of 50 participants each, with group 1 receiving carvedilol and group 2 receiving ACE inhibitors/angiotensin receptor blockers (ARB). After obtaining the baseline data and routine investigations on admission, all patients were followed up for a period of 6 months, with repeat Fasting and post-prandial blood sugar levels checked every 2 weeks and HbA1C levels rechecked at 3 and 6 months.

Results: Both groups of 50 participants each had approximately equal number of male (31 in group 1 vs 32 in group 2) and female patients (19 in group 1 vs 18 in group 2). Group 1 had 27 patients on insulin with a

reduction in mean dose of insulin from 54.89 ± 17.13 unit to 49.33 ± 16.87 unit, which was statistically significant (P < 0.05). Reduction in mean FBS, PP2BS and HbA1C levels after treatment was found to be significant.

Conclusions: In our study, Carvedilol was found out to be useful in reduction of fasting blood glucose level, HbA1C level and postprandial blood sugar level in patients with diabetes mellitus and hypertension. Carvedilol may offer advantages in patients with diabetes and hypertension by improving glucose metabolism.

Keywords: Carvedilol, Diabetes Mellitus, Hypertension, HbA1C

Introduction

Diabetes Mellitus and Hypertension are a major public health issue worldwide, and important modifiable risk factors for premature cardiovascular disease viz., coronary artery disease, heart failure and cerebrovascular disease[1]. Diabetes is estimated to affect 425 million people worldwide, with its estimated prevalence being 8.5 percent in the United States, 9.9 percent in Asians and 10.9 percent in the Chinese[(2-5)]. Type 2 diabetes makes up about 85-90% of all the cases of Diabetes Mellitus, and the prevalence is expected to increase substantially due to the marked increase in childhood obesity. According to the International Diabetes Foundation, Diabetes currently affects more than 62 million Indians, more than any other country in the world, with an average age of onset of 42.5 years. Nearly 1 million Indians die due to diabetes every year[2].

The global prevalence of hypertension has increased significantly from 31 percent of the world's adult population or 1.4 billion adults in 2010 to 1.8 billion individuals in 2017[6]. Individuals with hypertension are believed to have a two-fold higher risk of developing Coronary Artery Disease, four times higher risk of congestive heart failure, and seven times higher risk of cerebrovascular disease and stroke compared to normotensive subjects[7]. Hypertension occurs commonly in patients with diabetes, mainly because of extracellular fluid volume expansion, increased arterial stiffness and development of kidney disease [(8-9)]. The effective control of blood pressure in such patients reduces cardiovascular risk [10].

Beta blockers are not the first class of antihypertensive drugs recommended in patients with hypertension and diabetes mellitus, due to their effect of masking of hypoglycemic symptoms, insulin resistance and dyslipoproteinemia and possible worsening of peripheral artery disease. However, these adverse effects are absent or much less pronounced with carvedilol, a combined nonselective beta- and alpha-1 adrenergic antagonist, which has been found to be have certain advantages in patients with diabetes. The GEMINI trial compared the effect of two different beta blockers on glycemic control as well as other cardiovascular risk factors and demonstrated better stabilization of HbA1C, improved insulin resistance and slowed development of microalbuminuria with carvedilol as compared to metoprolol in the presence of RAS blockade [11].

The objective of our study is to see effect of Carvedilol in reducing insulin resistance, dose of Insulin and oral hypoglycaemic agents, and effect on HbA1C in patient with Diabetes Mellitus type 2 with hypertension. Our study demonstrates improvement of insulin resistance and differences in stabilization of glycemic control between carvedilol and metoprolol at doses needed to achieve BP goal.

Methodology

A prospective, observation study was carried out with a sample size of 100 patients in tertiary care hospital of South Gujarat for a period of 6 months. Patients with

diabetes mellitus type 2 and hypertension on insulin and/or oral hypoglycemic agents, willing to give consent were included in the study. These patients were divided into two groups viz. Group 1 receiving carvedilol and Group 2 receiving angiotensin converting enzyme (ACE) inhibitors / angiotensin receptor blocker(ARB).

History and physical examination findings were noted for all patients included in the study, with a special emphasis on presence/absence of all peripheral arterial pulsations, multiple blood pressure readings recorded in both the supine and standing position, heart rate calculated from an electrocardiogram (ECG). Other parameters of physical examination measured were height, weight, Body Mass Index, waist circumference, hip circumference, waist to hip ratio, ankle brachial pressure index and Vibration perception threshold (VPT) by vibrometer/ Digital Biothesiometer for peripheral arterial disease and diabetic peripheral neuropathy. Routine investigations were sent for all patients at the time of inclusion in the study. These included a complete blood count, urine routine microscopy, fundoscopic examination, lipid profile (total cholesterol and serum triglyceride), liver and renal function tests, fasting, Post-prandial blood sugar and HbA1C levels. A standard 12 lead electrocardiogram (ECG) was recorded for all patients. All patients were followed up for a period of 6 months, with repeat Fasting and Post-prandial blood sugar levels checked every 2 weeks and HbA1C levels rechecked at 3 and 6 months. Carvedilol was started in all patients in group 1 at 6.25 mg. The effect of carvedilol on FBS, PP2BS and HbA1C was monitored and its dose was gradually increased up to a maximum dose of 25 mg with a consequent reduction of insulin dose.

Results

Table 1: Frequency in both groups

Group	Frequency (percent)
Group 1	50 (50%)
Group 2	50 (50%)
Total	100

Table 1 shows that total 100 patients were included in this study, of which 50 patients were on carvedilol (group 1) and 50 patients were on ACEI/ARB (group2)

Table 2: Gender wise distribution of patients

	Group 1 (n = 50)	Group 2 (n = 50)
Male	31 (62%)	32 (64%)
Female	19 (38%)	18 (36%)
Male: female ratio	31:19	32:18
Mean age	55.5	54.8
SD	7.9	9.2
95 % CI	53.31-57.69	52.25-57.35

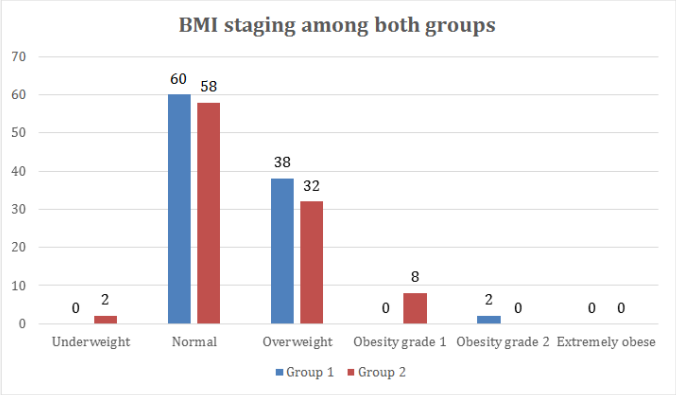
Table 2 shows that in group 1, out of 50 patients, 31 (62%) were males and 19 (38%) patients were females, whereas in group 2, out of 50 patients, 32 (64%) were males and 18 (36%) patients were females. In both groups proper proportion of male and female patients was maintained. Male to female ratio was 31:19 in carvedilol group which is comparable to ACE/ARB group (32:18). In group 1 mean age was 55.5 ± 7.9 years whereas in group 2, mean age was 54.8 ± 9.2 years. So in both groups mean age was comparable.

Table 3: BMI (Body Mass Index) staging among both groups

	BMI staging	Group 1 (n = 50)	Group 2 (n = 50)
Underweight	< 18.5	0 (0%)	1 (2%)

Normal	18.5 – 24.9	30 (60%)	29 (58%)
Overweight	25 – 29.9	19 (38%)	16 (32%)
Obesity grade 1	30 – 34.9	0 (0%)	4 (8%)
Obesity grade 2	35 – 39.9	1 (2%)	0 (0%)
Extremely obese	≥ 40	0 (0%)	0 (0%)
Mean		24.8	25.1
SD		2.8	2.7

Figure 1: Gender wise distribution of patients



As seen in table 3 and figure 1 , In group 1, out of 50 patients, 30 patient (60%) were in the group of BMI 18.5-24.9 followed by BMI 25-29.9 (19 patients)(38%). In group 2, 29 patient (58%) were in the group of BMI 18.5-24.9 followed by BMI 25-29.9 (16 patients)(32%).

Thus, in the both groups Maximum number of patients were from normal (18-24.9) and pre obese (25-29.9). Mean BMI was found to be 24.8±2.8 in carvedilol group and 25.1±2.7 in the ACE/ARB drug group.

Table 4: Waist circumference by WHO (World Health Organization)

	Waist circumference	Group 1 (n = 50)	Group 2 (n = 50)
Male n = 63	≤ 102 cm	30 (97%)	30 (94%)
	> 102 cm	1 (3%)	2 (6%)
Female n = 37	≤ 88 cm	15 (79%)	11 (61%)
	> 88 cm	4 (21%)	7 (39%)

When we measured waist circumference according to WHO South Asian region 2008 STEPS protocol criteria the results were as follows - In this study, in group 1 waist circumference is more in females (4 out of 19) (21%) (waist circumference >88cm) than males (3%) (1 out of 31) (waist circumference >102cm). In this study, in group 2 also waist circumference is more in females (7 out of 11) (39%) than males (2 out of 32) (6%). So overall in females waist circumference is more than males.

Table 5: Waist to hip ratio among patients by WHO criteria

	Waist to hip ratio	Group 1 (n = 50)	Group 2 (n = 50)
Male n = 63	≤ 0.9	29 (94%)	29 (91%)
	> 0.9	2 (6%)	3 (9%)
Female n = 37	≤ 0.85	14 (74%)	17 (94%)
	> 0.85	5 (26%)	1 (6%)

Waist to hip ratio was measured according WHO STEPS 2008 criteria. In group 1 waist to hip ratio is more among females (26%) (5 out of 19) (waist to hip ratio >0.85) than males (6%) (2 out of 31) (waist to hip ratio >0.9). In group 2 waist hip ratio was more among males (3 out of 32) (9%) than among females (1 out of 18) (6%). So in group 1 waist hip ratio was more in females than males whereas in group 2 waist hip ratio was more among males than females.

Table 6: Effect on dose of insulin after treatment

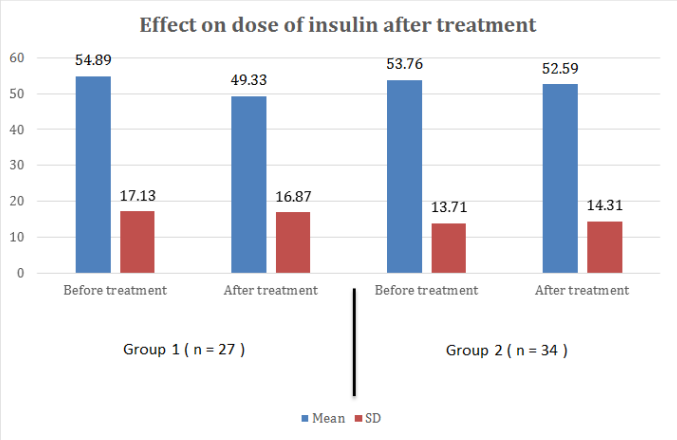
	Group 1 (n = 27)		Group 2 (n = 34)	
	Before treatment	After treatment	Before treatment	After treatment

Mean	54.89	49.33	52.67	51.78
SD	17.13	16.87	14.51	15.17
95 % CI	50.14 – 59.63	44.65 – 54.01		
p value	The value of t is -6.539355. The value of p is < .00001. The result is significant at p < .05.		The value of t is -1.279764. The value of p is < .21193. The result is *not* significant at p < .05.	

Before Treatment – 1st visit of patient for this study

After Treatment – At the end of treatment at six months

Figure 2: Effect on dose of insulin after treatment



In group 1 total 27 patients were on insulin and mean dose of insulin was 54.89 ± 17.13 unit but after treatment this dose reduced to 49.33 ± 16.87 unit and this reduction was found to be statistically significant (P<0.05). In group 2 total 27 patients were on insulin and mean dose of insulin was 52.67 ± 14.51 unit but after treatment this dose reduced to 51.78 ± 15.17unit BUT this reduction was NOT statistically significant (P<0.05). Thus, Insulin dose reduction was found to be significant among group 1 after treatment.

Table 7: Reduction in Fasting Blood Sugar

	Group 1 (n = 50)		Group 2 (n = 50)	
	Before treatment	After treatment	Before treatment	After treatment
Mean	176.36	106.5	203.28	110.58
SD	49.18	19.73	69.07	17.45
95 % CI	162.7 – 189.9	101.03 – 111.97	184.14 – 222.42	105.74 – 115.42
p value	The value of t is -12.197325. The value of p is < .00001. The result is significant at p < .05.		The value of t is -10.417502. The value of p is < .00001. The result is significant at p < .05.	

Before Treatment – 1st visit of patient for this study

After Treatment – At the end of treatment at six months

In group 1 mean FBS level was 176.36 ± 49.18 before treatment but after treatment, the mean FBS level decreased to 106.5 ± 19.73 and this reduction was found to be statistically significant (P<0.05). In group 2 mean FBS level was 203.28 ± 69.07 before treatment but after treatment, the mean FBS level decreased to 110.58 ± 17.45 and this reduction was found to be statistically significant (P<0.05). Thus, Reduction in Fasting blood sugar was found to be significant among both groups after the treatment. But in group 1 reduction in fasting blood sugar is more than group 2.

Table 8: Reduction in Postprandial Blood Sugar

	Group 1 (n = 50)		Group 2 (n = 50)	
	Before treatment	After treatment	Before treatment	After treatment
Mean	270.16	142.94	280.84	154.84
SD	79.66	30.58	85.05	30.21
95 % CI	248.08 – 292.24	134.46 – 151.42	257.27 – 304.41	146.47 – 163.21
p value	The value of t is -13.227776. The value		The value of t is -12.324495. The value	

	of p is < .00001. The result is significant at p < .05.	of p is < .00001. The result is significant at p < .05.

Before Treatment – 1st visit of patient for this study

After Treatment – At the end of treatment at six months

In group 1 mean PPBS level was 270.16 ± 79.66 before treatment but after treatment, the mean PP2BS level decreased to 142.94 ± 30.58 and this reduction was found to be statistically significant (P<0.05). In group 1 mean PP2BS level was 280.84 ± 85.05 before treatment but after treatment its level decreased to 154.84 ± 30.21 and this reduction was found to be statistically significant (P<0.05). Thus, Reduction in postprandial blood sugar was found to be significant among both groups after the treatment. But reduction in PP2BS was more in group 1 than group 2.

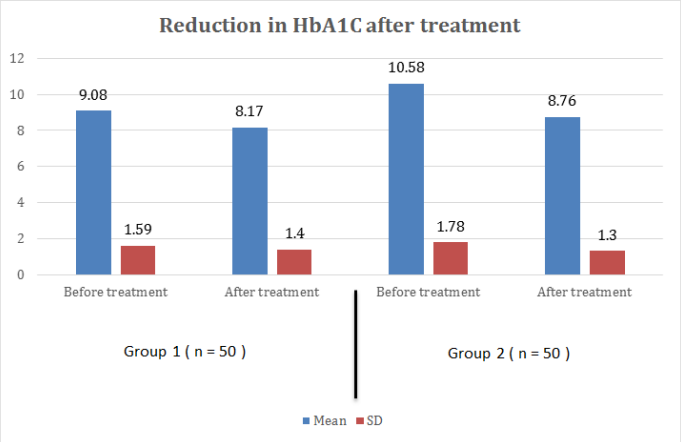
Table 9: HbA1C reduction after treatment

	Group 1 (n = 50)		Group 2 (n = 50)	
	Before treatment	After treatment	Before treatment	After treatment
Mean	9.08	8.17	10.58	8.76
SD	1.59	1.40	1.78	1.30
95 % CI	8.64 – 9.52	7.78 – 8.56	10.08 – 11.07	8.39 – 9.12
p value	The value of t is -12.533902. The value of p is < .00001. The result is significant at p < .05.		The value of t is -13.44945. The value of p is < .00001. The result is significant at p < .05.	

Before Treatment – 1st visit of patient for this study

After Treatment – At the end of treatment at six months

Figure 3: HbA1C reduction after treatment



In group 1 mean HbA1C level was 9.08 ± 1.59 before treatment but after treatment, the mean HbA1C level decreased to 8.17 ± 1.40 and this reduction was found to be statistically significant (P<0.05). In group 2 mean HbA1C level was 10.58 ± 1.78 before treatment but after treatment, the mean HbA1C level decreased to 8.76 ± 1.30 and this reduction was found to be statistically significant (P<0.05). Thus, Reduction in HbA1C was found to be significant after treatment in both groups.

Table 10: ABI (Ankle Brachial Index) among both groups of patients

	Group 1 (n = 50)		Group 2 (n = 50)	
ABI	Before treatment	After treatment	Before treatment	After treatment
1 - 1.4	25	29	14	24
0.9 - 1.0	13	11	11	9
0.8 - 0.9	5	6	3	5
0.5 - 0.8	7	4	12	12
Less than 0.5	0	0	0	0
Mean	0.94	1.04	0.89	0.94

SD	0.12	1.20	0.20	0.21
95% CI	0.90 - 0.97	0.71 - 1.37	0.83 - 0.94	0.88 - 0.99
paired t test p value	The value of t is 7.457379. The value of p is < .00001. The result is significant at p < .05.		The value of t is 5.035973. The value of p is < .00001. The result is significant at p < .05.	

Before Treatment – 1st visit of patient for this study

After Treatment – At the end of treatment at six months

In group 1, out of 50 patients 25 patient had ABI between 1 - 1.4 and 13 patients had ABI between 0.9 - 1.0 before treatment and mean ABI was 0.94 ± 0.12 which was increased after treatment to 1.04 ± 1.20 which was statistically significant. In group 2, out of 50 patients 14 had ABI between 1 - 1.4 and 11 patients had ABI between 0.9 - 1.0 before treatment and mean ABI was 0.94 ± 0.12 which was increased after treatment to 1.04 ± 1.20 which was statistically significant. Thus, Most of the patients (50%) have ABI between 1-1.4 before treatment and change in ABI is found to be significant in both groups after treatment.

Discussion

We conducted an observational study with 100 study participants in tertiary care hospital of south gujarat with two groups, one consist of 50 study participantns of DM type 2 with hypertention taking insulin/ oral hypoglcemic agents and carvedilol while other 50 study participants of type 2 DM with hypertention taking insulin/ oral hypoglcemic drug and ARB/ACE inhibitors.

In our study, gender and age wise distribution were comparable in between carvedilol (male: female= 31:19, AGE=55.5± 7.9) and ARB/ACE group (male: female= 32:18, AGE=54.8± 9.2). in a GEMINI trial by Barkis GL et al mean age in carvedilol and metoprolol group were 60.7±9.4 years and 61.1±9.7 years, while gender wise distribution in carvedilol group was (male:female=60.40)and in metoprolol group was (male:female=52.48)[11]. Body mass index was also comparable in both the group, mean BMI in carvedilol group was found to be 24.8±2.8 and 25.1±2.7 in ACE/ARB group. While in barkis GL et al, mean BMI in carvedilol group were 33.5±5.8 where as 33.7±6.2in metoprolol group[11].

We found that a total of 27 study participants were taking insulin for treatment of type 2 DM in group 1 and were given carvedilol for management of hypertention. Mean dose of insulin was reduced to 49.33+16.87 units from 54.89+17.13 units at the end of treatment in this study participants which was significant with p vaue of <0.05. Insulin dose reduction was also seen in other group taking ACE/ARB though it was not significant. Barkish GL et al found that Insulin sensitivity improved with carvedilol (–9.1%; P=.004) with significant difference of –7.2% (95% CI, –13.8% to –0.2%; P=.004) between two groups[11]. Similarly in a randomised controlled trial by Giugliano D et al, significant reduction in fasting insulin level was founf after treatment with carvedilol[12]. Similarly in jacob s et al, they found significant improvement in insulin sensitivity after treatment with carvedilol which was imapried at baseline[13].

Significant reduction in fasting blood glucose level was found in group 1 taking carvedilol as a treatmnet (176.36 ± 49.18 to 106.5 ± 19.73, P<0.05) and in group 2 taking ACE/ARB as a treatment (203.28 ± 69.07 to 110.58 ± 17.45, P<0.05). while in Ferrua S et al, mean fasting plasma glucose was at upper normal limits in baseline conditions and did not significantly change during carvedilol treatment (108±13 mg/dL versus 109±12 mg/dL, P =0 .895)[14]. In the study by Bank AJ at al, in

carvedilol group mean plasma fasting glucose level was reduced to 131±39 from 133±38 after treatment though reduction in FBS was not statistically significant[15]. In the study by Barkis GL et al, mean FBS level was 147 before treatment and increased to 154.7 after treatment in carvedilol group[11].

We also found that mean post pandrial blood sugar was reduced from 270.16 ± 79.66 to 142.94 ± 30.58 in patient taking carvedilol which was significant with p value of <0.05. Similarly in Ehmer B et al, mean PPBS level in Carvedilol group was 157.9±39.6, which was reduced to 156.1±41.2 after treatment[16]. In Giugliano D et al, they found increase in total glucose disposal, 9.54 µmol/kg of body weight per minute (95% CI, 7 to 11.9 µmol/kg per minute) in respionse to treatment with carvedilol[12].

In Study participants who were taking carvedilol, mean HbA1C level was 9.08 ± 1.59 before treatment but after treatment, the mean HbA1C level decreased to 8.17 ± 1.40 and this reduction was found to be statistically significant (P<0.05). Similarly in Ahmed A et al, in carvedilo drug group mean HbA1c level was 9.24 and at was reduced to 6.84 after treatment which was statistically significant[17]. Barkis GL et al, Carvedilol treatment had no effect on HbA1c (mean [SD] change from baseline to end point, 0.02% [0.04%]; 95% CI, –0.06% to 0.10%; P=0.65) [11].

Conclusion

We conducted a prospective observational study among 100 study participants having type2 DM and hypertension with 50 study participants in each group. Study participants were taking carvedilol and ACE/ARB inhibitors in Group 1 and group 2.

Hypertension and DM both are non-communicable disease and have various macro and micro vascular complications, when both existed together amplification of these complications occurs. In our study Carvedilol was found to be useful in reduction of fasting blood glucose level, HBA1C level and postprandial blood sugar level. We also found reduction in mean insulin requirement at the end of study in study participants taking Carvedilol. Carvedilol may offer advantages in patients with diabetes and hypertension by improving glucose metabolism.

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