Abstract
Hypertension is the commonest preventable cause of death among the diabetic patient. Current guidelines recommend using combination drug therapy in case of uncontrolled hypertension in diabetic patient. Even though, duel combinations are sometimes insufficient to achieve target blood pressure. Objective of this study was to evaluate the efficacy and safety of Indapamide and Carvedilol as third drug in controlling hypertension in diabetic patients. This prospective comparative study was conducted in 32 well controlled diabetic patient with uncontrolled hypertension those taking Olmesartan (20 mg/day) and Amlodipine (5 mg/day). Addition of both the drugs showed significant reduction of all the blood pressure parameters at the end of six weeks therapy without any major adverse effects. Systolic blood pressure decreased from 169.71±9.26 to 119.41±12.48 in Indapamide group (p<0.001) and 167.67±12.94 to 122.67±18.79 in Carvedilol group (p<0.001). Diastolic blood pressure decreased from 98.23±7.06 to 76.76±8.65 in Indapamide group (p<0.001) and 94.67±11.41 to 79.33±10.83 in Carvedilol group (p<0.001). Mean arterial pressure also reduced from 122.06±5.35 to 90.98±8.72 in Indapamide group (p<0.001) and 119.00±10.61 to 93.78±12.51 in Carvedilol group (p<0.001). Only ten patients suffered from mild adverse effects, such as epigastric discomfort, nausea, light headedness and drowsiness; which did not required stopping the therapy. Both the drugs are found to be equally effective as well as safe as third drug along with Olmesartan and Amlodipine in controlling hypertension in well controlled diabetic patients.

Keywords: Hypertension, Indapamide, Carvedilol, Efficacy, Safety.

Introduction
Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels1. The prevalence of hypertension is disproportionately high in patients suffering from diabetes,2 and individuals who have hypertension are nearly 2.5 times more likely to develop diabetes within 6 years than those without hypertension3,4. Hypertension is the most common preventable
cause of death, accounting for 7.5 million deaths in 2004. The relationship between increasing Blood Pressure (BP) and cardiovascular risk is well established with even modest changes in BP substantially increasing cardiovascular risk. Individuals who have hypertension, diabetes, and other related co morbidities are likely to need multiple antihypertensive agents to achieve the target BP goals recommended to these high-risk populations. Blocking two or more regulatory systems provides a more effective and more physiologic reduction in BP. Current guidelines also have recommended the use of combination therapy as first-line treatment, or early in the management of hypertension.

Fixed combination therapy is an efficacious, relatively safe, and may be cost-effective method to decrease BP in most patients with essential hypertension. Similar to other combinations, fixed-dose combination containing the dihydropyridine calcium channel blocker (CCB), Amlodipine, and the angiotensin II receptor blocker (ARB), Olmesartan, bring together two distinct and complementary mechanisms of action. This combination produced greater mean reduction in BP than either drug alone. Moreover addition of Olmesartan to Amlodipine decreased the Amlodipine-related adverse effects (peripheral edema). Even though, dual combinations are sometimes insufficient to achieve target BP those need a third drug.

However, recently the third generation β-blocker, Carvedilol, has been reported to possess characteristics different from the previously available non-selective and selective-blockers that have adverse effects on glucose and lipid metabolism. Nevertheless, little is known about the effects of co-administration of Carvedilol as the third agent with a combination of Renin-Angiotensin System (RAS) inhibitors and CCB on BP regulation and glucose metabolism. Hence this study was aimed to examine the safety and efficacy of adding either Carvedilol or Indapamide as a third drug on elevated blood pressure in well controlled type-II diabetic patient being treated with Olmesartan and Indapamide combination.

Materials and Methods

This study was a prospective comparative study among the well controlled diabetic patient with uncontrolled hypertension. This study was conducted at the Department of Pharmacology and Therapeutics, Sylhet MAG Osmani Medical College, and Diabetic Hospital, Sylhet between the period of July 2013 and June 2014. All Diabetic hypertensive patients aged 40 years and above, who failed to achieve target blood pressure with Olmesartan 20 mg/day and Amlodipine 5 mg/day for 8 weeks was included in this study. Patients with diabetic complications, secondary hypertension, and other co morbidities (such as malignant hypertension, arrhythmias, asthma, renal insufficiency etc.) were excluded.

The clinical histories of the patients were noted. Each patient was examined thoroughly. All the findings, previous history and reports and investigations were analyzed. Patients were screened for the exclusion criteria. BP was measured on same arm by the investigator using an appropriate cuff with a standard aneroid sphygmomanometer after at least 5 minutes of rest with the patient in the lying as per NICE/BHS guideline between 10.00 am to 1:00 pm in each working day. A mean of three recordings (each one minute apart) was taken. Heart rate was estimated after the third BP measurement. Routine haematological, bio-chemical, radiological and urine examination were done. A 12-channel ECG was performed to exclude cardiac abnormalities. Those who met the inclusion criteria were selected and met the exclusion criteria were excluded from the study. In this way 40 poorly control diabetic hypertensive patients were enrolled in this study.

Recruited patients were then divided randomly in group-A and group-B. The patients of group-A were treated with Indapamide 1.5 mg daily in single dose in the morning for 6 weeks and of group-B were treated with Carvedilol was given in dose of 12.5 mg twice daily as add-on treatment of ongoing Olmesartan 20 mg/day and Amlodipine 5 mg/day for 6 weeks. Follow up BP was measured and treatment related adverse effects were recorded at 2 weeks, 4 weeks and 6 weeks. All relevant data were recorded in preformed data collection sheet.

Quantitative data were expressed as mean and standard deviation and comparison was performed paired t test or repeated measure ANOVA and between groups by unpaired t test. Qualitative data were expressed as frequency and percentages and comparison was performed between two groups by Chi-Square (X²) test. Statistical analysis was performed by using SPSS (Statistical package for social science) for windows version 16.0. A probability value (p) of <0.05 was considered as significant.

Informal written consent was obtained from the patients after detailed explanation of the disease process and purpose of the study. Prior to the commencement of the study, the research protocol was approved by the Ethical Committee of Sylhet MAG Osmani Medical College, Sylhet.

Results

There were a total of 40 patients recruited in this study. In course of follow up period 3 patients from Indapamide group (due consent withdrawn one patient and failed to complete follow up two patients) and 5 patients from Carvedilol group (consent withdrawn one patient and failed to complete follow up four patients) were dropped out. So, per protocol analysis was done in 17 patients of Indapamide group and 15 patients of Carvedilol group. Both the groups are statistically similar in terms of their sex (X²=0.014; p>0.05) and age (t=-1.312; p>0.05).
Effect of Indapamide and Carvedilol as add on therapy on systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) showed in the Table I.

Table-I: Comparison of the effect of Indapamide or Carvedilol administered as add-on treatment on lying systolic blood pressure, diastolic blood pressure and mean arterial pressure estimated before and 2nd, 4th and 6th week of treatment.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Baseline</th>
<th>At 0 week</th>
<th>At 2nd week</th>
<th>At 4th week</th>
<th>At 6th week</th>
<th>p value</th>
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<tbody>
<tr>
<td>Systolic blood pressure (mean ± SD mm Hg)</td>
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<td></td>
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<tr>
<td>Indapamide group</td>
<td>169.71±9.26</td>
<td>127.94±12.25</td>
<td>118.82±12.48</td>
<td>119.41±12.48</td>
<td>119.41±12.48</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(n=17)</td>
<td>167.67±12.25</td>
<td>132.67±14.74</td>
<td>125.00±14.74</td>
<td>122.67±14.74</td>
<td>122.67±14.74</td>
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<tr>
<td>Carvedilol group</td>
<td>167.67±12.25</td>
<td>132.67±14.74</td>
<td>125.00±14.74</td>
<td>122.67±14.74</td>
<td>122.67±14.74</td>
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<tr>
<td>(n=15)</td>
<td>98.23±7.06</td>
<td>81.76±8.65</td>
<td>82.06±8.65</td>
<td>76.76±8.65</td>
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<td>p&lt;0.001</td>
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<td>Diastolic blood pressure (mean ± SD mm Hg)</td>
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<tr>
<td>Indapamide group</td>
<td>98.23±7.06</td>
<td>81.76±8.65</td>
<td>82.06±8.65</td>
<td>76.76±8.65</td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(n=17)</td>
<td>94.67±8.65</td>
<td>87.33±9.82</td>
<td>81.00±9.82</td>
<td>79.33±9.82</td>
<td></td>
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<tr>
<td>Carvedilol group</td>
<td>94.67±8.65</td>
<td>87.33±9.82</td>
<td>81.00±9.82</td>
<td>79.33±9.82</td>
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<td></td>
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<tr>
<td>(n=15)</td>
<td>112.06±5.35</td>
<td>97.16±6.83</td>
<td>94.31±6.83</td>
<td>90.98±6.83</td>
<td></td>
<td>p&lt;0.001</td>
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<tr>
<td>Mean arterial pressure (mean ± SD mm Hg)</td>
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<tr>
<td>Indapamide group</td>
<td>112.06±5.35</td>
<td>97.16±6.83</td>
<td>94.31±6.83</td>
<td>90.98±6.83</td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>(n=17)</td>
<td>119.00±10.61</td>
<td>102.44±12.51</td>
<td>95.67±12.51</td>
<td>93.78±12.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol group</td>
<td>119.00±10.61</td>
<td>102.44±12.51</td>
<td>95.67±12.51</td>
<td>93.78±12.51</td>
<td></td>
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</tr>
<tr>
<td>(n=15)</td>
<td>±5.35</td>
<td>±8.63</td>
<td>±9.82</td>
<td>±8.72</td>
<td></td>
<td>p=0.001</td>
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</table>

Data were expressed as mean±SD; n: Number of the subject; SD: Standard deviation; p: probability value

Mean of the baseline SBP in these groups were 169.71±9.26 and 167.67±12.25 mm of Hg, which gradually decreased to 119.41±12.48 and 122.67±18.79 mm of Hg at the end of 6th week. Mean of the DBP at baseline were 98.23±7.06 and 94.67±11.41 mm of Hg that reduced to 76.76±8.65 and 79.33±10.83 mm of Hg respectively. Similar reduction also observed in MAP; from 122.06±5.35 to 93.78±12.51 mm of Hg from 119.00±10.61 to 92.78±12.51 mm of Hg among the respective group. However, variation of the parameters from baseline to the end of 2nd week, 4th week and 6th week within the respective group were found to be significant statistically; while intergroup variations at baseline, 2nd week, 4th week and 6th week between the study groups were not significant.

Percentage changes in SBP, DBP and MAP of the Indapamide and Carvedilol groups showed in Figure 1 to 3. Overall difference of SBP from baseline to end of the research was found to be significant in Indapamide group (F=3.735, df=2, p<0.005), while insignificant in Carvedilol group (F=2.015, df=2, p>0.05). Similar result also observed in DBP; p-value in Indapamide group was <0.05 (F=2.659, df=2) and in Carvedilol group was >0.05 (F=3.625, df=2). On the other hand, opposite result observed in case of MAP. Overall difference from baseline to end point of treatment was insignificant in Indapamide group (F=3.215, df=2, p>0.05) while significant in Carvedilol group (F=4.510, df=2, p<0.05).

However, percentage changes between the study groups at 2nd, 4th and 6th week were found to be insignificant in all statistics except two occasions. The p-value for SBP of Indapamide group compared to Carvedilol group were >0.05 (t=-1.130, 95% CI,-10.616 to 3.055) at 2nd week, >0.05 (t=0.966, 95% CI,14.900 to 5.330) at 4th week and >0.05 (t=-0.735, 95% CI,-10.618 to 5.000) at 6th week. The p-value for DBP of Indapamide group compared to Carvedilol group were <0.05 (t=-2.278, 95% CI -17.982 to -9.82) at 2nd week, >0.05 (t=0.510, 95% CI,15.137 to 2.645) at 4th week and >0.05 (t=-1.435, 95% CI,-15.137 to 2.645) at 6th week of treatment. The p-value for MAP in comparison between Indapamide group and Carvedilol group were <0.05 (t=-2.216, 95% CI -12.961 to 0.530) at 2nd week, >0.05 (t=-0.844, 95% CI -11.424 to 4.742) at 4th week and >0.05 (t=-1.361, 95% CI,-11.285 to 2.260) at 6th week of treatment.

There were very few patients experienced drug adverse effects, which were mild in nature and does not require
stopping the therapy. In Indapamide treated group, six (35.3%) patients experienced adverse effect; while in Carvedilol treated group, four (26.4%) patients experienced adverse effect. There was no statistical significant difference between the groups in respect to the adverse effects (p>0.05). The recorded adverse effects were almost similar in both groups such as epigastric discomfort [1 (5.9%) vs 0 (0.0%); p>0.05], nausea [2 (11.8%) vs 3 (20.0%); p>0.05], light headedness [3 (17.6%) vs 0 (0.0%); p>0.05] and drowsiness [0 (0.0%) vs 1 (6.7%); p>0.05].

Some clinical trials recently documented that only 30-50% of patients with hypertension actually achieved a BP goal of <140/90 mm Hg. Patients with multiple organ damages usually have hypertension that is difficult to control. In such cases, the use of a single antihypertensive agent is insufficient to lower BP13. Thus, the latest British Hypertension Society14 and European Society of Hypertension guidelines16 indicate that renin-angiotensin system (RAS) inhibitors, such as angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme (ACE) inhibitors, are the first-line agents to reduce BP and the rate of decline in renal function13. Recent studies demonstrating equivalent clinical outcomes of ACE inhibitors and ARBs17,18. As second-line agents, CCB are widely used for the prevention of organ damage. If a combination of the two at the usual doses is ineffective, increasing the dose of either ACE inhibitors or CCB to the maximum dose may be the next option. However, renal insufficiency increases the risk of adverse drug reactions by dose elevation13. Dual combinations do not achieve BP control in 15-20% of patients, and it is estimated that three antihypertensive agents are needed to achieve BP control in approximately 25% of patients16,19. Therefore, adding thiazide-like diuretics [such as Chlortalidone (12.5-25.0 mg once daily) or Indapamide (1.5 mg modified-release or 2.5 mg once daily)] is suitable as a third-line agent introduced at Step 314. In a study Kereiakes et al20 compared the efficacy and tolerability of triple-combination treatment with Olmesartan 40 mg, Amlodipine 10 mg and Hydrochlorothiazide 25 mg versus the component dual-combination treatments (Olmesartan 40 mg and Amlodipine 10 mg, Olmesartan 40 mg and Hydrochlorothiazide 25 mg, Amlodipine 10 mg and Hydrochlorothiazide 25) in patients with moderate-to-severe hypertension. The triple combination resulted in a significantly greater percentage of patients achieving BP goal at weeks 6, 8, 10, and 12 (with week 6 representing 2 weeks on triple-combination therapy); p < 0.001 for all comparisons).

Adding another class of medication would be an alternative strategy, although the guidelines do not indicate clearly the third choice for uncontrolled hypertension. In these patients, β-blockers seem to be more effective than increasing the dose of either ACE inhibitors or CCB13. National Collaborating Centre for Chronic Conditions21 recommended an alpha blocker or beta blocker should be added to third agent.

In the present study systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were decreased significantly from initiation of treatment to the end point of treatment of 6 weeks in both Indapamide treated group and Carvedilol treated group; but no significant difference was observed between two treatment groups. Yasuda et al13 found that both SBP and DBP was reduced in combination therapy of Carvedilol, Olmesartan and Amlodipine treated group.

This study also showed that the percentage reduction of lying SBP (-29.32% vs -26.51%; p>0.05); DBP (-21.52% vs -15.28%) and MAP was (-23.35% vs -20.84%; p>0.05) did not differ significantly in Indapamide treated group compared to Carvedilol treated group estimated at 6th week of treatment. Kereiakes et al20 reported triple combination of Olmesartan, Amlodipine and Hydrochlorothiazide in participants with hypertension and diabetes, chronic kidney disease, or chronic cardiovascular disease lowered BP effectively. Oparil et al22 found that long-term efficacy of a combination of Amlodipine and Olmesartan Medoxomil ± Hydrochlorothiazide in patients with hypertension stratified by age, race and diabetes status was effectively reduced BP.

In Indapamide treated group, 6 (35.3%) patients experienced adverse effect; while in Carvedilol treated group, 4 (26.4%) patients experienced adverse effect. There was no statistical significant difference between the groups in respect to the adverse effects (p>0.05). Adverse effects reported in our study were mild and well tolerated and no discontinuation was needed. Several previous studies also showed well tolerability of triple drug combination13,20.

Conclusion

Addition of either Indapamide (1.5 mg/d) or Carvedilol (25 mg/d) as a third drug along with Olmesartan (20 mg/day) and Amlodipine (5mg/day) in uncontrolled hypertension in controlled diabetic patients were found to be equally effective and safe in this study. However, the authors like to recommend conducting clinical trial involving larger number of patients for a longer period of follow up in order to have more reliable result.
Acknowledgement

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References


