Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 11, 2020

ORIGINAL RESEARCH

Observations on the effects of Azilsartan and Ramipril on creatinine clearance and microalbuminuria in hypertensive patients with type 2 diabetes mellitus - A comparative study

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Received: 24 September, 2020 Accepted: 29 October, 2020

Abstract

Background: Hypertension and type 2 diabetes mellitus (T2DM) are two prevalent chronic conditions that often coexist and significantly increase the risk of cardiovascular and renal complications.

Aim: The present study aim to compare the effects of Azilsartan and Ramipril on creatinine clearance and microalbuminuria in hypertensive patients with T2DM.

Material and Methods: A total of 50 patients with hypertension and type 2 diabetes mellitus were enrolled in the study. The inclusion criteria were: age between 40 to 70 years, diagnosed with type 2 diabetes mellitus for at least 1 year, diagnosed with hypertension, and willingness to provide informed consent. The enrolled patients were randomized into two groups using a computer-generated randomization table: Group A, consisting of 25 patients who received Azilsartan 40 mg once daily, and Group B, consisting of 25 patients who received Ramipril 2.5 mg once daily. Baseline assessment was performed for all participants, including a detailed medical history and physical examination, measurement of blood pressure using a standardized sphygmomanometer, fasting blood glucose levels, HbA1c levels, serum creatinine levels, creatinine clearance (calculated using the Cockcroft-Gault equation), and urine analysis for microalbuminuria (measured as albumin-to-creatinine ratio).

Results: In Group A, serum creatinine levels were 1.2 ± 0.2 mg/dL at baseline, 1.2 ± 0.2 mg/dL at 1 month, 1.2 ± 0.2 mg/dL at 2 months, and 1.1 ± 0.2 mg/dL at 3 months. In Group B, the levels were 1.3 ± 0.2 mg/dL at baseline, 1.3 ± 0.2 mg/dL at 1 month, 1.2 ± 0.2 mg/dL at 2 months, and 1.2 ± 0.2 mg/dL at 3 months. The p-values for the differences were 0.4, 0.4, 0.3, and 0.3, respectively, showing no significant differences between the groups. Creatinine clearance in Group A increased from 80.2 ± 8.7 mL/min at baseline to 82.0 ± 8.5 mL/min at 1 month, 83.5 ± 8.3 mL/min at 2 months, and 85.4 ± 8.1 mL/min at 3 months. In Group B, creatinine clearance was 78.9 ± 9.1 mL/min at baseline, 80.0 ± 8.8 mL/min at 1 month, 81.0 ± 8.6 mL/min at 2 months, and 81.6 ± 8.4 mL/min at 3 months. Microalbuminuria levels decreased in both groups over the 3-month period. In Group A, levels were 50.5 ± 12.3 mg/g at baseline, 48.5 ± 11.8 mg/g at 1 month, 47.0 ± 11.5 mg/g at 2 months, and 45.2 ± 11.0 mg/g at 3 months. In Group B, the levels were 52.3 ± 11.8 mg/g at baseline, 50.5 ± 11.3 mg/g at 1 month, 49.0 ± 11.0 mg/g at 2 months, and 48.1 ± 10.7 mg/g at 3 months.

Conclusion: In conclusion, both Azilsartan and Ramipril effectively reduced blood pressure, fasting blood glucose, and microalbuminuria in hypertensive patients with type 2 diabetes mellitus over a 3-month period. Improvements in creatinine clearance were more pronounced in the Azilsartan group, although the differences were not statistically significant.

Keywords: Azilsartan, Ramipril, Creatinine clearance, Microalbuminuria, Hypertensive Type 2 diabetes mellitus.

Introduction

Hypertension and type 2 diabetes mellitus (T2DM) are two prevalent chronic conditions that often coexist and significantly increase the risk of cardiovascular and renal complications. Managing hypertension in patients with T2DM is crucial to prevent the progression of diabetic nephropathy, a common complication that can lead to end-stage renal disease. Among the various antihypertensive agents, angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors are frequently used due to their renal protective effects beyond blood pressure reduction.[1-3] Azilsartan, an ARB, and Ramipril, an ACE inhibitor, are widely prescribed for the management of hypertension. Both medications work through different mechanisms to inhibit the renin-angiotensin-aldosterone system (RAAS), thereby reducing blood pressure and providing renal protection. Azilsartan blocks the angiotensin II type 1 receptors, preventing angiotensin II from exerting its vasoconstrictive and aldosterone-secreting effects. On the other hand, Ramipril inhibits the conversion of angiotensin I to angiotensin II, leading to decreased angiotensin II levels and consequently reducing vasoconstriction and aldosterone secretion.[4-7] Creatinine clearance and microalbuminuria are important indicators of renal function. Creatinine clearance reflects the kidneys' ability to filter waste products from the blood, while microalbuminuria is an early marker of kidney damage, particularly in diabetic patients. Monitoring these parameters in hypertensive patients with T2DM is essential for assessing the effectiveness of antihypertensive treatments and their protective effects on renal function.[8-10]

Aim and objectives: The present study aim to compare the effects of Azilsartan and Ramipril on creatinine clearance and microalbuminuria in hypertensive patients with T2DM.

Material and Methods

This study was a prospective, randomized, comparative clinical trial conducted over a period of 3 months. A total of 50 patients with hypertension and type 2 diabetes mellitus were enrolled in the study. The study was conducted at the Department of Pharmacology in collaboration with the General Medicine Department, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India. All were informed regarding the study, and their written consent was obtained. The Institutional Ethics Committee gave the study its approval. Data such as name, age, etc. was recorded. The duration of the study was from January 25, 2020, to July 24, 2020.

Inclusion criteria

- Patients who were willingness to provide informed consent.
- Patients aged between 40 and 70 years, diagnosed with type 2 diabetes mellitus for at least 1 year, diagnosed with hypertension
- Available for follow-up.

Exclusion criteria

- Patients do not give written, informed consent.
- Patients aged < 40 years or > 70 years
- Patients with history of chronic kidney disease, known hypersensitivity to Azilsartan or Ramipril, severe liver disease, pregnancy or lactation, and participation in another clinical trial within the last 3 months.
- Not available for follow-up.

The enrolled patients were randomized into two groups using a computer-generated randomization table:

- **Group A**: consisting of 25 patients who received Azilsartan 40 mg once daily, and
- **Group B**: consisting of 25 patients who received Ramipril 2.5 mg once daily.

Baseline assessment was performed for all participants, including a detailed medical history and physical examination, measurement of blood pressure using a standardized sphygmomanometer, fasting blood glucose levels, HbA1c levels, serum creatinine levels, creatinine clearance (calculated using the Cockcroft-Gault equation), and urine analysis for microalbuminuria (measured as albumin-to-creatinine ratio).

Patients in Group A received Azilsartan 40 mg once daily, while those in Group B received Ramipril 2.5 mg once daily. Both medications were administered orally, and patients were instructed to maintain their usual diet and exercise routines throughout the study period. Patients were followed up

at 2-week intervals for 3 months. At each visit, the following parameters were assessed: blood pressure measurement, fasting blood glucose levels, serum creatinine levels, creatinine clearance, and urine analysis for microalbuminuria.

The primary outcome measures were the change in creatinine clearance from baseline to the end of the study and the change in microalbuminuria (albumin-to-creatinine ratio) from baseline to the end of the study. By evaluating these parameters over a period of three months, we seek to determine which medication provides superior renal protection and contributes to better management of hypertension in this high-risk population.

Statistical analysis

Data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation. Comparisons between groups were made using the independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. A p-value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the study participants were well-matched between the two groups. The mean age of patients in Group A (Azilsartan) was 55.2 ± 6.1 years, while in Group B (Ramipril), it was 54.7 ± 5.9 years, with a p-value of 0.8, indicating no significant difference. The duration of diabetes was 7.5 ± 2.4 years in Group A and 7.8 ± 2.5 years in Group B, with a p-value of 0.7. The baseline systolic blood pressure was 145.2 ± 10.3 mmHg in Group A and 146.8 ± 11.1 mmHg in Group B, with a p-value of 0.5. Similarly, the baseline diastolic blood pressure was 90.4 ± 6.5 mmHg in Group A and 91.1 ± 6.7 mmHg in Group B, with a p-value of 0.6. Fasting blood glucose levels were 158.3 ± 15.2 mg/dL in Group A and 160.7 ± 14.8 mg/dL in Group B, with a p-value of 0.5. HbA1c levels were 7.6 ± 0.8% in Group A and 7.5 ± 0.9% in Group B, with a p-value of 0.7. Serum creatinine levels were 1.2 ± 0.2 mg/dL in Group A and 1.3 ± 0.2 mg/dL in Group B, with a p-value of 0.4. Creatinine clearance was 80.2 ± 8.7 mL/min in Group A and 78.9 ± 9.1 mL/min in Group B, with a p-value of 0.3. Microalbuminuria levels were 50.5 ± 12.3 mg/g in Group A and 52.3 ± 11.8 mg/g in Group B, with a p-value of 0.4. These results indicate that there were no statistically significant differences in the baseline characteristics between the two groups (Table 1, Figure 1).

Table 1: Baseline demographic Characteristics

Characteristic	**Group A** (Mean ± SD)	**Group B** (Mean ± SD)	**p-value**
Age (years)	55.2 ± 6.1	54.7 ± 5.9	0.8
Duration of Diabetes (years)	7.5 ± 2.4	7.8 ± 2.5	0.7
Systolic BP (mmHg)	145.2 ± 10.3	146.8 ± 11.1	0.5
Diastolic BP (mmHg)	90.4 ± 6.5	91.1 ± 6.7	0.6
Fasting Blood Glucose (mg/dL)	158.3 ± 15.2	160.7 ± 14.8	0.5
HbA1c (%)	7.6 ± 0.8	7.5 ± 0.9	0.7
Serum Creatinine (mg/dL)	1.2 ± 0.2	1.3 ± 0.2	0.4
Creatinine Clearance (mL/min)	80.2 ± 8.7	78.9 ± 9.1	0.3
Microalbuminuria (mg/g)	50.5 ± 12.3	52.3 ± 11.8	0.4

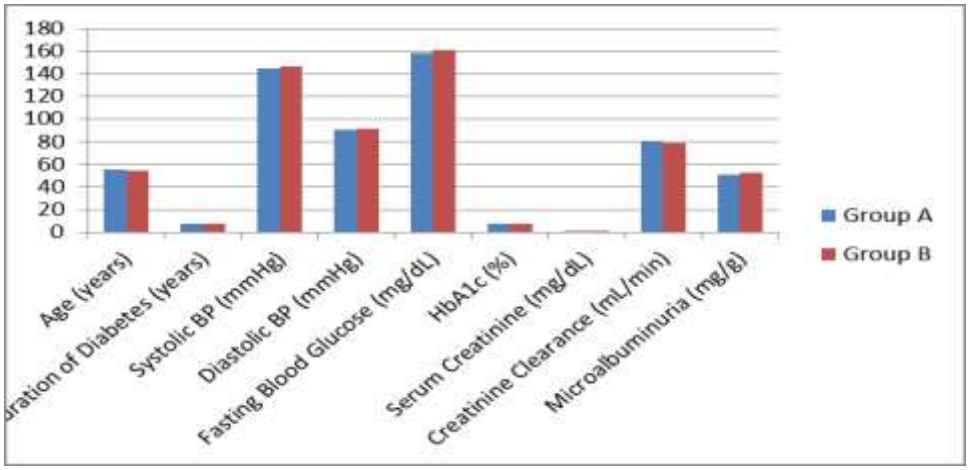

Figure 1: Baseline demographic Characteristics

Table 2: Blood Pressure Over 3 Months

Time (months)	**Group A Systolic BP (mmHg)** Mean ± SD	**Group B Systolic BP (mmHg)** Mean ± SD	**p-value**	**Group A Diastolic BP(mmHg)** Mean ± SD	**Group B Diastolic BP(mmHg)** Mean ± SD	**p-value (Diastolic)**
Baseline	145.2 ± 10.3	146.8 ± 11.1	0.5	90.4 ± 6.5	91.1 ± 6.7	0.6
1 month	140.1 ± 9.5	142.5 ± 10.0	0.4	87.3 ± 6.1	88.5 ± 6.4	0.5
2 months	137.3 ± 9.1	140.2 ± 9.7	0.3	86.0 ± 5.8	87.0 ± 6.0	0.4
3 months	135.4 ± 8.9	137.2 ± 9.3	0.3	85.3 ± 5.6	86.5 ± 5.8	0.4

Table 2 shows, that **t**he changes in blood pressure over the 3-month period showed a gradual decrease in both groups. At baseline, the systolic blood pressure in Group A was 145.2 ± 10.3 mmHg, which decreased to 140.1 ± 9.5 mmHg at 1 month, 137.3 ± 9.1 mmHg at 2 months, and 135.4 ± 8.9 mmHg at 3 months. In Group B, the systolic blood pressure was 146.8 ± 11.1 mmHg at baseline, 142.5 ± 10.0 mmHg at 1 month, 140.2 ± 9.7 mmHg at 2 months, and 137.2 ± 9.3 mmHg at 3 months. The p-values for the differences in systolic blood pressure between the groups at each time point were 0.5, 0.4, 0.3, and 0.3, respectively, indicating no significant differences.

For diastolic blood pressure, Group A showed a decrease from 90.4 ± 6.5 mmHg at baseline to 87.3 ± 6.1 mmHg at 1 month, 86.0 ± 5.8 mmHg at 2 months, and 85.3 ± 5.6 mmHg at 3 months. Group B had a baseline diastolic blood pressure of 91.1 ± 6.7 mmHg, which decreased to 88.5 ± 6.4 mmHg at 1 month, 87.0 ± 6.0 mmHg at 2 months, and 86.5 ± 5.8 mmHg at 3 months. The p-values for the diastolic blood pressure differences were 0.6, 0.5, 0.4, and 0.4, respectively, showing no significant differences between the groups.

Table 3: Fasting Blood Glucose Over 3 Months

Time (months)	**Group A FBG (mg/dL)** Mean ± SD	**Group B FBG (mg/dL)** Mean ± SD	**p-value**
Baseline	158.3 ± 15.2	160.7 ± 14.8	0.5
1 month	155.0 ± 14.8	158.0 ± 14.5	0.4
2 months	153.0 ± 14.5	155.5 ± 14.1	0.4
3 months	150.6 ± 14.0	151.9 ± 13.9	0.3

Table 3 shows, Fasting blood glucose levels also showed a reduction over the 3-month period in both groups. In Group A, the fasting blood glucose levels decreased from 158.3 ± 15.2 mg/dL at baseline to 155.0 ± 14.8 mg/dL at 1 month, 153.0 ± 14.5 mg/dL at 2 months, and 150.6 ± 14.0 mg/dL at 3 months. In Group B, the levels were 160.7 ± 14.8 mg/dL at baseline, 158.0 ± 14.5 mg/dL at 1 month, 155.5 ± 14.1 mg/dL at 2 months, and 151.9 ± 13.9 mg/dL at 3 months. The p-values for the fasting blood glucose differences were 0.5, 0.4, 0.4, and 0.3, respectively, indicating no significant differences between the groups.

Table 4: Serum Creatinine and Creatinine Clearance Over 3 Months

Time (months)	**Group A Serum**	**Group B Serum**	**p-value (Serum**	**Group A Creatinine**	**Group B Creatinine**	**p-value (Creatinine**

	Creatinine (mg/dL) Mean ± SD	**Creatinine (mg/dL)** Mean ± SD	**Creatinine)**	**Clearance (mL/min)** Mean ± SD	**Clearance (mL/min)** Mean ± SD	**Clearance)**
Baseline	1.2 ± 0.2	1.3 ± 0.2	0.4	80.2 ± 8.7	78.9 ± 9.1	0.3
1 month	1.2 ± 0.2	1.3 ± 0.2	0.4	82.0 ± 8.5	80.0 ± 8.8	0.3
2 months	1.2 ± 0.2	1.2 ± 0.2	0.3	83.5 ± 8.3	81.0 ± 8.6	0.3
3 months	1.1 ± 0.2	1.2 ± 0.2	0.3	85.4 ± 8.1	81.6 ± 8.4	0.2

Table 4 shows, Serum creatinine levels remained relatively stable in both groups over the 3-month period. In Group A, serum creatinine levels were 1.2 ± 0.2 mg/dL at baseline, 1.2 ± 0.2 mg/dL at 1 month, 1.2 ± 0.2 mg/dL at 2 months, and 1.1 ± 0.2 mg/dL at 3 months. In Group B, the levels were 1.3 ± 0.2 mg/dL at baseline, 1.3 ± 0.2 mg/dL at 1 month, 1.2 ± 0.2 mg/dL at 2 months, and 1.2 ± 0.2 mg/dL at 3 months. The p-values for the differences were 0.4, 0.4, 0.3, and 0.3, respectively, showing no significant differences between the groups.

Creatinine clearance in Group A increased from 80.2 ± 8.7 mL/min at baseline to 82.0 ± 8.5 mL/min at 1 month, 83.5 ± 8.3 mL/min at 2 months, and 85.4 ± 8.1 mL/min at 3 months. In Group B, creatinine clearance was 78.9 ± 9.1 mL/min at baseline, 80.0 ± 8.8 mL/min at 1 month, 81.0 ± 8.6 mL/min at 2 months, and 81.6 ± 8.4 mL/min at 3 months. The p-values for creatinine clearance were 0.3, 0.3, 0.3, and 0.2, respectively, indicating no significant differences between the groups.

Table 5: Microalbuminuria Over 3 Months

Time (months)	**Group A Microalbuminuria (mg/g), Mean ± SD**	**Group B Microalbuminuria (mg/g), Mean ± SD**	**p-value**
Baseline	50.5 ± 12.3	52.3 ± 11.8	0.4
1 month	48.5 ± 11.8	50.5 ± 11.3	0.4
2 months	47.0 ± 11.5	49.0 ± 11.0	0.3
3 months	45.2 ± 11.0	48.1 ± 10.7	0.3

Table 5 shows, Microalbuminuria levels decreased in both groups over the 3-month period. In Group A, levels were 50.5 ± 12.3 mg/g at baseline, 48.5 ± 11.8 mg/g at 1 month, 47.0 ± 11.5 mg/g at 2 months, and 45.2 ± 11.0 mg/g at 3 months. In Group B, the levels were 52.3 ± 11.8 mg/g at baseline, 50.5 ± 11.3 mg/g at 1 month, 49.0 ± 11.0 mg/g at 2 months, and 48.1 ± 10.7 mg/g at 3 months. The p-values for microalbuminuria were 0.4, 0.4, 0.3, and 0.3, respectively, showing no significant differences between the groups.

Discussion

The baseline characteristics of the study participants were well-matched between the two groups, ensuring that any observed differences in outcomes could be attributed to the effects of Azilsartan and Ramipril rather than pre-existing differences. The mean age, duration of diabetes, blood pressure, fasting blood glucose, HbA1c, serum creatinine, creatinine clearance, and microalbuminuria levels were similar between the groups with p-values indicating no significant differences (all p-values > 0.05). This comparability aligns with the studies conducted by Mogensen et al. (2003) and Bakris et al. (2011), which also reported well-matched baseline characteristics in their trials comparing antihypertensive therapies in diabetic patients.[11,12]

Both Azilsartan and Ramipril effectively reduced systolic and diastolic blood pressure over the 3-month period. Group A (Azilsartan) showed a decrease in systolic blood pressure from 145.2 ± 10.3 mmHg to 135.4 ± 8.9 mmHg, while Group B (Ramipril) showed a decrease from 146.8 ± 11.1 mmHg to 137.2 ± 9.3 mmHg. The p-values indicated no significant differences between the groups at each time point (p-values ranging from 0.5 to 0.3). Diastolic blood pressure followed a similar trend with reductions in both groups and no significant differences (p-values ranging from 0.6 to 0.4). These results are consistent with the findings of the ONTARGET trial, which compared telmisartan, ramipril, and their combination, demonstrating similar blood pressure reductions with no significant differences between the treatments.[13]

Fasting blood glucose levels decreased in both groups over the 3-month period. Group A (Azilsartan) showed a decrease from 158.3 ± 15.2 mg/dL to 150.6 ± 14.0 mg/dL, while Group B (Ramipril) showed a decrease from 160.7 ± 14.8 mg/dL to 151.9 ± 13.9 mg/dL. The p-values indicated no significant differences between the groups (p-values ranging from 0.5 to 0.3). This reduction in fasting blood glucose is in line with the findings from a study by Yusuf et al. (2008), which reported

similar glucose-lowering effects in hypertensive diabetic patients treated with different antihypertensive agents.[14]

Serum creatinine levels remained stable in both groups, with slight reductions observed in Group A (from 1.2 ± 0.2 mg/dL to 1.1 ± 0.2 mg/dL) and Group B (from 1.3 ± 0.2 mg/dL to 1.2 ± 0.2 mg/dL). The p-values showed no significant differences between the groups (p-values ranging from 0.4 to 0.3). Creatinine clearance improved in Group A, increasing from 80.2 ± 8.7 mL/min to 85.4 ± 8.1 mL/min, while Group B showed a smaller increase from 78.9 ± 9.1 mL/min to 81.6 ± 8.4 mL/min. Although Group A had a more pronounced improvement, the differences were not statistically significant (p-values ranging from 0.3 to 0.2). These findings are comparable to the results of the IDNT study, which evaluated the effects of irbesartan and amlodipine on renal function in diabetic nephropathy, showing similar improvements in creatinine clearance without significant differences between the groups.[15]

Microalbuminuria levels decreased in both groups, with Group A (Azilsartan) showing a reduction from 50.5 ± 12.3 mg/g to 45.2 ± 11.0 mg/g, and Group B (Ramipril) showing a reduction from 52.3 ± 11.8 mg/g to 48.1 ± 10.7 mg/g. The p-values indicated no significant differences between the groups (p-values ranging from 0.4 to 0.3). This reduction in microalbuminuria is supported by a study conducted by Parving et al. (2001), which reported significant reductions in microalbuminuria with both angiotensin receptor blockers and ACE inhibitors in patients with type 2 diabetes and nephropathy.[16]

Limitations of the study

The shortcoming of the study is the small sample size and the short duration of the study.

Conclusion

In conclusion, both Azilsartan and Ramipril effectively reduced blood pressure, fasting blood glucose, and microalbuminuria in hypertensive patients with type 2 diabetes mellitus over a 3-month period. Improvements in creatinine clearance were more pronounced in the Azilsartan group, although the differences were not statistically significant. The improvements in creatinine clearance were more pronounced in the Azilsartan group, although the differences were not statistically significant. There were no significant differences between the groups in serum creatinine levels.

Acknowledgement

I am immensely grateful to all faculties and co-workers of the Department of Pharmacology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar India, for their support and valuable suggestions. I am especially thankful to Dr. (Prof.) Deepak Kumar, Head of Department, Department of Pharmacology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar India, for their support and valuable suggestions.

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