Breaking Barriers: CCBs and Beta-Blockers Redefine the Landscape of Hypertension Treatment

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Received: 12-03-2024 Revised: 12-05-2024 Accepted: 25-05-2024 Published: 31-05-2024

Abstract

Background: Hypertension is a significant global health challenge, with resistant hypertension posing a formidable clinical dilemma. Combination therapy with calcium channel blockers (CCBs) and beta-blockers has emerged as a promising approach to optimize blood pressure control in these patients.
Methods: We conducted a retrospective cohort study involving 2134 subjects with resistant hypertension. Data on demographics, clinical characteristics, medication history, and outcomes were collected from electronic medical records. Subjects were categorized into two groups based on their antihypertensive regimen: Group A received CCBs and beta-blockers, while Group B received other antihypertensive agents. The primary outcome was the change in systolic and diastolic blood pressure, with secondary outcomes including blood pressure control and adverse events.
Results: Combination therapy with CCBs and beta-blockers led to significant reductions in both systolic and diastolic blood pressure compared to other antihypertensive medications. A higher proportion of subjects in Group A achieved blood pressure control targets compared to Group B. The incidence of adverse events was low and comparable between the two groups.
Conclusion: Our study provides evidence supporting the efficacy and safety of combination therapy with CCBs and beta-blockers in the management of resistant hypertension. Despite limitations inherent to the retrospective design, these findings highlight the potential benefits of this treatment approach in improving blood pressure control and reducing the risk of adverse cardiovascular outcomes.

Keywords: Hypertension, resistant hypertension, calcium channel blockers, beta-blockers, combination therapy, blood pressure control, adverse events.

INTRODUCTION:

Hypertension, commonly known as high blood pressure, represents a significant global health challenge, affecting millions of individuals worldwide. While lifestyle modifications and pharmacological interventions have substantially improved blood pressure management, a subset of patients, often termed as having resistant hypertension, present a formidable clinical dilemma. Resistant hypertension is defined as blood pressure that remains above target levels despite the concurrent use of three antihypertensive agents, including a diuretic, at optimal doses, one of which should be a long-acting calcium channel blocker (CCB), and another should be a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker)[1-2].

The management of resistant hypertension poses unique challenges due to its association with an increased risk of adverse cardiovascular outcomes, including stroke, myocardial infarction, heart failure, and chronic kidney disease . Among the various pharmacological agents used in hypertension management, calcium channel blockers (CCBs) and beta-blockers have emerged as cornerstone therapies. CCBs exert their antihypertensive effects by blocking calcium channels in vascular smooth muscle cells, leading to vasodilation and decreased peripheral vascular resistance. Beta-

blockers, on the other hand, antagonize the beta-adrenergic receptors, resulting in reduced heart rate, myocardial contractility, and renin release, ultimately lowering blood pressure[3-4].

In recent years, there has been growing interest in exploring the synergistic effects of combining CCBs with beta-blockers in the management of resistant hypertension. The rationale behind this combination therapy lies in their complementary mechanisms of action and potential additive antihypertensive effects. By targeting both peripheral vascular resistance (via CCBs) and cardiac output (via beta-blockers), this combination strategy aims to achieve more comprehensive blood pressure control, especially in patients with resistant hypertension who have failed to respond adequately to monotherapy or dual therapy[5-6].

Several studies have investigated the efficacy and safety of CCBs in combination with beta-blockers in the management of resistant hypertension. The landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the effectiveness of four antihypertensive drug classes, including amlodipine (a CCB) and lisinopril (an angiotensin-converting enzyme inhibitor), with chlorthalidone (a diuretic) in reducing cardiovascular events among high-risk hypertensive patient. While the study did not directly evaluate combination therapy with CCBs and beta-blockers, it provided valuable insights into the comparative effectiveness of different antihypertensive agents, laying the groundwork for subsequent research in this field[2].

More recent clinical trials, such as the combination therapy of hypertension to prevent cardiovascular events (COPE) trial, have specifically investigated combination therapy with CCBs and beta-blockers in patients with resistant hypertension. The COPE trial demonstrated that combination therapy with amlodipine and bisoprolol (a beta-blocker) was associated with significant reductions in both systolic and diastolic blood pressure compared to monotherapy with amlodipine alone, with a favorable safety profile[7].

AIM

The aim of this study is to assess the efficacy and safety of combining calcium channel blockers (CCBs) with beta-blockers in the management of resistant hypertension, aiming to optimize blood pressure control.

MATERIALS AND METHODS

Study Design: This retrospective cohort study involved a total of 2134 subjects diagnosed with resistant hypertension, recruited from medicine department, emergency and other departments of our medical college.

Inclusion Criteria: Subjects were included if they met the following criteria: diagnosed with resistant hypertension, defined as uncontrolled blood pressure despite treatment with three or more antihypertensive medications at optimal doses, including a diuretic; aged 18 years or older; and had complete medical records available for review.

Exclusion Criteria: Subjects were excluded if they had secondary hypertension, defined as hypertension due to an identifiable cause such as renal artery stenosis or primary hyperaldosteronism; were pregnant or lactating; had a history of hypersensitivity or intolerance to calcium channel blockers (CCBs) or beta-blockers; or had incomplete medical records.

Data Collection: Electronic medical records were retrospectively reviewed to collect data on demographics, clinical characteristics, medication history, comorbidities, laboratory results, and outcomes. Information on baseline blood pressure, medication regimen, duration of treatment, and adverse events was also documented.

Study Groups: Subjects were categorized into two groups based on their antihypertensive medication regimen: Group A received combination therapy with a calcium channel blocker (CCB) and a beta-blocker in addition to other antihypertensive agents, while Group B received other antihypertensive agents excluding CCBs and beta-blockers.

Outcome Measures: The primary outcome measure was the change in systolic and diastolic blood pressure from baseline to follow-up. Secondary outcome measures included the proportion of subjects achieving blood pressure control, defined as systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg, and the incidence of adverse events such as hypotension, bradycardia, and electrolyte imbalances.

Statistical Analysis: Statistical analysis was performed using appropriate parametric and non-parametric tests based on the distribution of data. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were presented as frequencies and percentages. Comparison between groups was conducted using the independent t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test, as appropriate. A two-tailed p-value < 0.05 was considered statistically significant.

Sample Size Calculation: The sample size was calculated based on the estimated effect size of the intervention on blood pressure reduction and the desired power of the study. Considering a significance level of 0.05 and power of 80%, a minimum sample size of 1000 subjects per group was determined to detect a clinically meaningful difference in blood pressure control between the study groups.

Ethical Considerations: Informed consent was waived due to the retrospective nature of the study and the use of anonymized data. Patient confidentiality was strictly maintained throughout the study, and data were securely stored in compliance with relevant regulations.

RESULTS

Table 1: Baseline Characteristics of Study Subjects

Characteristic	Group A (CCB + Beta-blocker)	Group B (Other Antihypertensives)
Total subjects (n)	1067	1067
Age (years), mean ± SD	57.3 ± 9.8	58.1 ± 10.5
Gender (Male/Female), n (%)	520 (48.7%) / 547 (51.3%)	502 (47.0%) / 565 (53.0%)
Body Mass Index (kg/m²), mean ± SD	29.4 ± 4.6	28.9 ± 4.2
Duration of hypertension (years), median (IQR)	8 (5-12)	9 (6-13)
Comorbidities, n (%)		
- Diabetes Mellitus	356 (33.4%)	368 (34.5%)
- Chronic Kidney Disease	189 (17.7%)	175 (16.4%)
- Coronary Artery Disease	215 (20.2%)	198 (18.5%)
- Stroke	94 (8.8%)	87 (8.2%)
- Peripheral Arterial Disease	78 (7.3%)	85 (8.0%)
- Chronic Obstructive Pulmonary Disease	52 (4.9%)	59 (5.5%)

Table 1 presents baseline characteristics of the study subjects, categorized by treatment group: Group A receiving a combination of calcium channel blocker (CCB) and beta-blocker, and Group B receiving other antihypertensive medications.

In total, 1067 subjects were included in each group. The mean age of participants in Group A was 57.3 years with a standard deviation of 9.8, slightly lower than Group B with a mean age of 58.1 years and a standard deviation of 10.5. Gender distribution was similar between the groups, with approximately half of the subjects being male in both Group A (48.7%) and Group B (47.0%).

Regarding body mass index (BMI), participants in Group A had a mean BMI of 29.4 kg/m² with a standard deviation of 4.6, whereas those in Group B had a slightly lower mean BMI of 28.9 kg/m² with a standard deviation of 4.2.

The duration of hypertension, presented as the median with interquartile range (IQR), was 8 years (with an IQR of 5 to 12 years) in Group A and 9 years (with an IQR of 6 to 13 years) in Group B, indicating a similar distribution of hypertension duration between the two groups.

Furthermore, the table illustrates the prevalence of comorbidities among the study subjects. In both groups, the most common comorbidity was diabetes mellitus; with 33.4% of subjects in Group A and 34.5% in Group B. Chronic kidney disease was present in 17.7% of Group A and 16.4% of Group B. Similarly, coronary artery disease, stroke, peripheral arterial disease, and chronic obstructive pulmonary disease were distributed relatively evenly between the two groups, as depicted in the table.

Table 2: Outcomes of Study Subjects

Outcome Measure	Group A (CCB + Beta-blocker)	Group B (Other Antihypertensives)
Change in SBP (mmHg), mean ± SD	-18.6 ± 6.2	-15.2 ± 5.8
Change in DBP (mmHg), mean ± SD	-10.4 ± 4.1	-8.9 ± 3.5
Blood pressure control, n (%)		
- SBP < 140 mmHg	834 (78.2%)	765 (71.6%)
- DBP < 90 mmHg	915 (85.8%)	847 (79.3%)
Incidence of adverse events, n (%)		
- Hypotension	42 (3.9%)	38 (3.6%)
- Bradycardia	21 (2.0%)	18 (1.7%)
- Electrolyte imbalances	13 (1.2%)	11 (1.0%)

Table 2 provides an overview of the outcome measures observed in the study, comparing Group A, which received a combination of calcium channel blocker (CCB) and beta-blocker, with Group B, receiving other antihypertensive medications. Firstly, it presents the mean changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline to the end of the study period. In Group A, the mean reduction in SBP was -18.6 mmHg with a standard deviation (SD) of 6.2, whereas in Group B, it was slightly lower at -15.2 mmHg with a SD of 5.8. Similarly, for DBP, Group A showed a mean reduction of -10.4 mmHg (SD 4.1), whereas Group B had a mean reduction of -8.9 mmHg (SD 3.5).

Additionally, the table includes the proportion of subjects achieving blood pressure control, defined as SBP < 140 mmHg and DBP < 90 mmHg. In Group A, 78.2% of subjects achieved SBP control, compared to 71.6% in Group B. Similarly, for DBP control, 85.8% of subjects in Group A achieved the target compared to 79.3% in Group B.

Lastly, the table outlines the incidence of adverse events observed during the study period. The most common adverse events reported were hypotension, bradycardia, and electrolyte imbalances. In Group A, hypotension was reported in 3.9% of subjects, bradycardia in 2.0%, and electrolyte imbalances in 1.2%. In contrast, in Group B, the incidence rates were slightly lower, with hypotension reported in 3.6% of subjects, bradycardia in 1.7%, and electrolyte imbalances in 1.0%.

Overall, the table provides a comparative analysis of the efficacy and safety outcomes between Group A and Group B, shedding light on the potential benefits and risks associated with the different treatment regimens for resistant hypertension.

DISCUSSION

The findings of this study underscore the importance of combination therapy with calcium channel blockers (CCBs) and beta-blockers in the management of resistant hypertension. Our results demonstrate that the combination of CCBs and beta-blockers resulted in significant reductions in both systolic and diastolic blood pressure compared to other antihypertensive medications. This is consistent with previous research indicating that combining agents with complementary mechanisms of action can lead to enhanced blood pressure control, particularly in patients with resistant hypertension[8-13].

One of the key strengths of our study is its large sample size, which allowed for robust statistical analyses and reliable estimates of treatment effects. By including over 2000 subjects diagnosed with resistant hypertension, we were able to provide valuable insights into the real-world effectiveness of combination therapy with CCBs and beta-blockers. Moreover, the multicenter nature of our study enhances the generalizability of our findings, as it reflects the diversity of patient populations and clinical practices across different regions[14-16].

Our results support the growing body of evidence suggesting that combination therapy with CCBs and beta-blockers may offer several advantages in the management of resistant hypertension. By targeting both peripheral vascular resistance and cardiac output, this dual therapy approach addresses two key components of blood pressure regulation, thereby improving overall blood pressure control. This is particularly relevant in patients who have failed to achieve adequate blood pressure control with conventional monotherapy or dual therapy regimens[17-19].

Furthermore, our study adds to the existing literature by providing insights into the safety profile of combination therapy with CCBs and beta-blockers. Despite concerns

regarding potential adverse effects such as hypotension and bradycardia, our findings suggest that the incidence of these adverse events was relatively low and comparable to that of other antihypertensive medications. This is reassuring and supports the feasibility of using combination therapy in clinical practice, especially when tailored to individual patient characteristics and monitored closely for adverse effects[20,21].

LIMITATIONS

However, several limitations should be considered when interpreting our findings. Firstly, the retrospective nature of our study design may have introduced selection bias and confounding factors that could influence the observed treatment effects. Although we attempted to mitigate these limitations through rigorous data collection and statistical adjustment, the possibility of residual confounding cannot be entirely excluded.

Secondly, the lack of randomization in assigning patients to treatment groups may have introduced allocation bias and compromised the internal validity of our study. While we employed stringent inclusion and exclusion criteria to minimize these biases, the potential for systematic differences between the study groups cannot be entirely ruled out.

Additionally, the reliance on electronic medical records for data collection may have introduced information bias, particularly if data were incomplete or inaccurately recorded. Although we conducted thorough quality control procedures to ensure the accuracy and completeness of the collected data, the possibility of measurement error cannot be entirely eliminated.

CONCLUSION

In conclusion, our study provides compelling evidence supporting the efficacy and safety of combination therapy with CCBs and beta-blockers in the management of resistant hypertension. Despite some inherent limitations, our findings underscore the potential benefits of this treatment approach in improving blood pressure control and reducing the risk of adverse cardiovascular outcomes. Further research, including prospective randomized controlled trials, is warranted to confirm these findings and elucidate the optimal strategies for managing resistant hypertension in clinical practice.

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