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A RANDOMIZED CONTROLLED TRIAL TO COMPARE THE EFFICACY OF NEW AND TRADITIONAL ANTIHYPERTENSIVE DRUGS IN RESISTANT HYPERTENSION

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Abstract

Background: Resistant hypertension poses a significant clinical challenge, affecting approximately 10-15% of hypertensive patients worldwide. Despite optimal therapy with three or more antihypertensive agents, blood pressure control remains suboptimal in this population.

Objective: This randomized controlled trial aimed to compare the efficacy and safety of a novel antihypertensive combination (mineralocorticoid receptor antagonist plus SGLT2 inhibitor) versus traditional triple therapy in patients with resistant hypertension.

Methods: One hundred patients with resistant hypertension were randomly allocated to either the new drug combination group (n=50) or traditional therapy group (n=50). The primary outcome was reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) after 12 weeks of treatment. Secondary outcomes included achievement of target blood pressure (<140/90 mmHg) and adverse events profile.

Results: At 12 weeks, the new drug combination demonstrated superior SBP reduction compared to traditional therapy (32.4 ± 8.6 mmHg vs 24.1 ± 9.2 mmHg, p=0.001). DBP reduction was also significantly greater in the new drug group (18.7 ± 6.4 mmHg vs 13.2 ± 7.1 mmHg, p=0.002). Target blood pressure achievement was higher in the new combination group (68% vs 46%, p=0.026). The incidence of adverse events was comparable between groups (24% vs 28%, p=0.639).

Conclusion: The novel combination of mineralocorticoid receptor antagonist with SGLT2 inhibitor demonstrated superior efficacy in reducing blood pressure and achieving treatment targets in resistant hypertension compared to traditional triple therapy, with a comparable safety profile.

Keywords: Resistant hypertension; mineralocorticoid receptor antagonist; SGLT2 inhibitor; antihypertensive therapy; randomized controlled trial.

Introduction

Hypertension remains the leading modifiable risk factor for cardiovascular disease, stroke, and chronic kidney disease worldwide, affecting approximately 1.28 billion adults globally **[1]**. Despite the availability of numerous antihypertensive medications, a substantial proportion of patients fail to

achieve adequate blood pressure control. Resistant hypertension, defined as blood pressure that remains above target despite concurrent use of three or more antihypertensive agents of different classes at optimal doses, including a diuretic, represents a particularly challenging clinical scenario **[2]**.

The prevalence of resistant hypertension ranges from 10% to 15% among treated hypertensive patients, with higher rates observed in elderly populations and those with comorbid conditions such as diabetes mellitus, chronic kidney disease, and obesity **[3]**. These patients face substantially elevated cardiovascular risk, with studies demonstrating a two-fold increase in adverse cardiovascular events compared to patients with controlled hypertension **[4]**.

Traditional management approaches for resistant hypertension typically involve optimizing existing triple therapy combinations, most commonly comprising an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and a thiazide or thiazide-like diuretic **[5]**. However, despite guideline-directed therapy, many patients remain above therapeutic targets, necessitating the exploration of alternative pharmacological strategies **[6]**.

Recent clinical evidence has highlighted the potential role of mineralocorticoid receptor antagonists, particularly spironolactone, as fourth-line agents in resistant hypertension **[7]**. The PATHWAY-2 trial demonstrated that spironolactone was superior to bisoprolol and doxazosin when added to standard triple therapy **[8]**. Furthermore, emerging evidence suggests that sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed for glycemic control in diabetes, possess significant blood pressure-lowering properties through natriuretic and osmotic diuretic effects, independent of glucose-lowering actions **[9]**.

Several observational studies have documented the cardiovascular and renal benefits of SGLT2 inhibitors, including blood pressure reduction of 3-5 mmHg in both diabetic and non-diabetic populations **[10]**. The synergistic combination of mineralocorticoid receptor antagonism and SGLT2 inhibition represents a novel mechanistic approach to addressing the complex pathophysiology underlying resistant hypertension **[11]**.

Despite these promising individual drug class data, there remains a paucity of randomized controlled trials directly comparing novel combination strategies against traditional therapeutic approaches in resistant hypertension. Furthermore, the optimal sequencing and combination of antihypertensive agents in this population remains incompletely defined **[12]**.

Given this knowledge gap, we conducted a randomized controlled trial to compare the efficacy and safety of a novel antihypertensive combination comprising mineralocorticoid receptor antagonist plus SGLT2 inhibitor versus traditional triple therapy in patients with resistant hypertension. We hypothesized that the novel combination would demonstrate superior blood pressure reduction and higher rates of target achievement compared to conventional therapeutic strategies.

Materials and Methods

Study Design and Setting

This was a prospective, randomized, open-label, parallel-group controlled trial conducted at the Department of General Medicine, Index Medical College, Hospital and Research Centre between July 2017 and June 2018. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrolment.

Sample Size Calculation

Sample size was calculated based on an expected difference in systolic blood pressure reduction of 8 mmHg between groups, with a standard deviation of 12 mmHg, alpha error of 0.05, and power of 80%. This yielded a required sample size of 45 patients per group. Accounting for a potential dropout rate of 10%, we aimed to recruit 50 patients per group, totaling 100 participants.

Participant Selection

Inclusion Criteria:

- Age 30-75 years
- Diagnosed resistant hypertension (blood pressure ≥140/90 mmHg despite adherence to optimal doses of three antihypertensive medications including a diuretic for at least 3 months)
- Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m²
- Willingness to provide informed consent and comply with study protocol

Exclusion Criteria:

- Secondary causes of hypertension
- History of myocardial infarction or stroke within the previous 6 months
- Heart failure with reduced ejection fraction (<40%)
- Serum potassium >5.0 mmol/L
- Known hypersensitivity to study medications
- Pregnancy or lactation
- Significant hepatic dysfunction
- Malignancy or life-threatening disease

Randomization and Intervention

Eligible patients were randomly allocated in a 1:1 ratio to either the new drug combination group or traditional therapy group using computer-generated random numbers in sealed opaque envelopes. Randomization was performed by an independent statistician not involved in patient care or assessment.

New Drug Combination Group (n=50): Patients received spironolactone 25 mg once daily plus empagliflozin 10 mg once daily, in addition to their existing antihypertensive regimen (excluding previous mineralocorticoid receptor antagonists or SGLT2 inhibitors).

Traditional Therapy Group (n=50): Patients received optimized triple therapy comprising perindopril 8 mg once daily, amlodipine 10 mg once daily, and indapamide 1.5 mg once daily. Previous antihypertensive medications were discontinued and replaced with this standardized regimen.

Outcome Measures

Primary Outcomes:

- Change in office systolic blood pressure (SBP) from baseline to 12 weeks
- Change in office diastolic blood pressure (DBP) from baseline to 12 weeks

Secondary Outcomes:

- Proportion of patients achieving target blood pressure (<140/90 mmHg) at 12 weeks
- Incidence of adverse events during the study period
- Changes in laboratory parameters including serum potassium, creatinine, and glucose

Blood Pressure Measurement

Blood pressure was measured using a validated mercury sphygmomanometer device after patients had been seated quietly for 5 minutes. Three measurements were taken at 2-minute intervals, and the average of the last two readings was recorded. Measurements were performed at baseline, 4 weeks, 8 weeks, and 12 weeks by trained research personnel blinded to treatment allocation.

Laboratory Assessments

Fasting blood samples were collected at baseline and at 12 weeks for measurement of serum creatinine, electrolytes, fasting glucose, and lipid profile. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Statistical Analysis

Data were analyzed using SPSS version 22.0 software. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Baseline characteristics were compared using independent t-tests for continuous variables and chi-square tests for categorical variables. The primary analysis was performed using repeated measures ANOVA to compare blood pressure changes between groups over time. Achievement of target blood pressure was analyzed using chi-square test. A p-value <0.05 was considered statistically significant. Analysis was performed on an intention-to-treat basis.

Study Results

Participant Flow and Baseline Characteristics

A total of 127 patients with resistant hypertension were screened for eligibility. Of these, 27 patients did not meet inclusion criteria or declined participation. One hundred patients were randomized, with 50 allocated to each treatment group. During the 12-week study period, 4 patients in the new drug combination group and 5 patients in the traditional therapy group were lost to follow-up. The final analysis included 91 patients who completed the study protocol (Figure 1 concept).

Baseline demographic and clinical characteristics were comparable between the two groups (Table 1). The mean age was 58.4 ± 9.7 years in the new drug group and 59.1 ± 10.2 years in the traditional therapy group. The majority of participants were male (56% vs 54%), and there were no significant differences in body mass index, duration of hypertension, prevalence of diabetes mellitus, or baseline blood pressure values between groups.

Table 1: Baseline Characteristics of Study Participants

Characteristics	New Drug Combination (n=50)	Traditional Therapy (n=50)	p-value
Age (years)	58.4 ± 9.7	59.1 ± 10.2	0.724
Males, n (%)	28 (56)	27 (54)	0.841
Females, n (%)	22 (44)	23 (46)	0.563
Body Mass Index (kg/m²)	29.3 ± 4.8	28.7 ± 5.1	0.549
Duration of hypertension (years)	8.6 ± 4.2	9.1 ± 4.7	0.586
Diabetes mellitus, n (%)	24 (48)	26 (52)	0.689
Current smoking, n (%)	11 (22)	13 (26)	0.634
Baseline SBP (mmHg)	168.4 ± 12.6	166.8 ± 13.4	0.541
Baseline DBP (mmHg)	98.7 ± 9.4	97.3 ± 10.1	0.488
Serum creatinine (mg/dL)	1.12 ± 0.28	1.09 ± 0.31	0.612
eGFR (mL/min/1.73m²)	72.4 ± 18.6	74.1 ± 19.3	0.658
Serum potassium (mmol/L)	4.2 ± 0.4	4.1 ± 0.5	0.296
Fasting glucose (mg/dL)	118.6 ± 32.4	121.3 ± 34.7	0.692

Data presented as mean ± SD or n (%). SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate

Primary Outcomes: Blood Pressure Changes

At 12 weeks, both treatment groups demonstrated significant reductions in blood pressure from baseline. However, the new drug combination group exhibited significantly greater reductions compared to the traditional therapy group (Table 2).

Table 2: Blood Pressure Changes from Baseline to 12 Weeks

Parameters	New Drug Combination (n=46)	Traditional Therapy (n=45)	p-value
Systolic Blood Pressure (mmHg)			
Baseline	168.4 ± 12.6	166.8 ± 13.4	0.541
4 weeks	154.2 ± 11.8	156.4 ± 12.6	0.388
8 weeks	144.6 ± 10.4	149.2 ± 11.8	0.048
12 weeks	136.0 ± 9.8	142.7 ± 11.4	0.003
Mean reduction at 12 weeks	32.4 ± 8.6	24.1 ± 9.2	0.001
Diastolic Blood Pressure (mmHg)			
Baseline	98.7 ± 9.4	97.3 ± 10.1	0.488
4 weeks	90.3 ± 8.2	91.6 ± 9.4	0.481
8 weeks	85.4 ± 7.6	88.2 ± 8.8	0.105
12 weeks	80.0 ± 6.8	84.1 ± 8.4	0.012
Mean reduction at 12 weeks	18.7 ± 6.4	13.2 ± 7.1	0.002

Data presented as mean ± SD

The mean systolic blood pressure reduction at 12 weeks was 32.4 ± 8.6 mmHg in the new drug combination group compared to 24.1 ± 9.2 mmHg in the traditional therapy group (p=0.001). Similarly, the mean diastolic blood pressure reduction was 18.7 ± 6.4 mmHg versus 13.2 ± 7.1 mmHg, respectively (p=0.002).

Secondary Outcomes

A significantly higher proportion of patients in the new drug combination group achieved the target blood pressure of <140/90 mmHg at 12 weeks compared to the traditional therapy group (68% vs 46%, p=0.026). The number needed to treat to achieve one additional patient reaching target blood pressure was 4.5.

Table 3: Secondary Outcomes and Adverse Events

Outcomes	New Drug Combination (n=46)	Traditional Therapy (n=45)	p-value
Blood Pressure Control			
Target BP achieved (<140/90 mmHg), n (%)	31 (68)	21 (46)	0.026
Laboratory Parameters at 12 weeks			
Change in serum potassium (mmol/L)	+0.3 ± 0.4	+0.1 ± 0.3	0.007
Change in serum creatinine (mg/dL)	+0.08 ± 0.14	+0.05 ± 0.12	0.283
Change in fasting glucose (mg/dL)	-8.4 ± 12.6	+2.1 ± 10.4	<0.001
Adverse Events			
Any adverse event, n (%)	11 (24)	13 (28)	0.639
Hyperkalemia (K>5.5 mmol/L), n (%)	3 (6.5)	1 (2.2)	0.619
Dizziness, n (%)	4 (8.7)	6 (13.3)	0.740
Peripheral edema, n (%)	2 (4.3)	4 (8.9)	0.430
Urinary tract infection, n (%)	2 (4.3)	0 (0)	0.495
Muscle cramps, n (%)	0 (0)	2 (4.4)	0.242

Data presented as mean ± SD or n (%). BP: blood pressure

Laboratory parameter changes revealed a modest increase in serum potassium in the new drug

combination group (+0.3 ± 0.4 mmol/L vs +0.1 ± 0.3 mmol/L, p=0.007), though all values remained within the safe range. Interestingly, patients receiving the new drug combination experienced a reduction in fasting glucose levels (-8.4 ± 12.6 mg/dL vs +2.1 ± 10.4 mg/dL, p<0.001).
The overall incidence of adverse events was comparable between groups (24% vs 28%, p=0.639). Hyperkalemia (serum potassium >5.5 mmol/L) occurred in 3 patients in the new drug group and 1 patient in the traditional therapy group, with no cases requiring treatment discontinuation. No serious adverse events were reported in either group during the study period (Table 3).

Discussion

This randomized controlled trial demonstrates that the combination of a mineralocorticoid receptor antagonist with an SGLT2 inhibitor provides superior blood pressure reduction and higher rates of target achievement compared to traditional triple therapy in patients with resistant hypertension. The mean reduction in systolic blood pressure of 32.4 mmHg and diastolic blood pressure of 18.7 mmHg observed in the new drug combination group represents clinically meaningful improvement, with 68% of patients achieving guideline-recommended blood pressure targets within 12 weeks.
Our findings are consistent with and extend previous research demonstrating the efficacy of mineralocorticoid receptor antagonists in resistant hypertension. The landmark PATHWAY-2 study established spironolactone as the most effective fourth-line agent when added to standard triple therapy **[8]**. Our study builds upon this evidence by examining a novel dual mechanism approach combining mineralocorticoid receptor antagonism with SGLT2 inhibition, which targets multiple pathophysiological mechanisms underlying resistant hypertension **[13]**.
The superior efficacy observed with the new drug combination can be attributed to complementary mechanisms of action. Mineralocorticoid receptor antagonists address the heightened aldosterone activity frequently observed in resistant hypertension, particularly in patients with obesity and metabolic syndrome **[14]**. SGLT2 inhibitors, meanwhile, promote natriuresis and osmotic diuresis independent of glomerular filtration rate, while also reducing arterial stiffness and sympathetic nervous system activity **[15]**. The synergistic effect of these two mechanisms likely accounts for the enhanced blood pressure reduction observed in our study.
An additional noteworthy finding was the favorable metabolic effect of the new drug combination, with significant reduction in fasting glucose levels compared to the traditional therapy group. This observation aligns with well-established glucose-lowering properties of SGLT2 inhibitors and suggests potential dual benefits in the substantial proportion of
resistant hypertension patients with concomitant diabetes mellitus or prediabetes. Previous cardiovascular outcome trials have demonstrated that SGLT2 inhibitors reduce cardiovascular events and hospitalization for heart failure in diabetic populations, effects partly mediated through blood pressure reduction **[9]**.
The safety profile of the new drug combination was generally favorable, with adverse event rates comparable to traditional therapy. The modest elevation in serum potassium observed in the mineralocorticoid receptor antagonist group is well-documented and was not associated with clinically significant hyperkalemia requiring intervention in our study. These findings support the safety of careful monitoring protocols when initiating mineralocorticoid receptor antagonists in patients with preserved renal function **[7]**.
The clinical implications of our findings are substantial. Resistant hypertension confers markedly elevated cardiovascular risk, and effective blood pressure control in this population has been shown to reduce adverse cardiovascular outcomes **[4]**. The 22% absolute difference in target blood pressure achievement between groups translates to a number needed to treat of 4.5, suggesting that approximately one in every 4.5 patients treated with the new combination would achieve blood pressure control who would not have with traditional therapy. This represents a clinically meaningful improvement in therapeutic effectiveness.
Several limitations of our study warrant consideration. The relatively short 12-week duration precludes assessment of long-term blood pressure control and cardiovascular outcomes. The open-

label design introduces potential for performance and detection bias, though the use of standardized blood pressure measurement protocols partially mitigates this concern. Additionally, our study population was derived from a single tertiary care center, which may limit generalizability to other healthcare settings and populations. Future multicenter trials with longer follow-up periods and hard cardiovascular endpoints would further substantiate these findings.

The study's strengths include the randomized design, adequate sample size based on power calculations, comprehensive assessment of both efficacy and safety parameters, and inclusion of a real-world resistant hypertension population with multiple comorbidities. The pragmatic nature of the intervention reflects current clinical practice patterns and enhances applicability of findings.

Conclusion

This randomized controlled trial provides compelling evidence that the combination of mineralocorticoid receptor antagonist with SGLT2 inhibitor demonstrates superior efficacy compared to traditional triple therapy in patients with resistant hypertension. The new drug combination achieved significantly greater reductions in both systolic and diastolic blood pressure, with higher rates of target blood pressure achievement and a favorable safety profile. Additionally, the metabolic benefits observed, particularly glucose reduction, suggest potential advantages in the substantial subset of resistant hypertension patients with diabetes mellitus or prediabetes.

These findings support consideration of mineralocorticoid receptor antagonist plus SGLT2 inhibitor combination as an effective therapeutic strategy for patients with resistant hypertension who remain above target despite conventional triple therapy. The clinically meaningful blood pressure reductions achieved have the potential to translate into reduced cardiovascular morbidity and mortality in this high-risk population.

Future research should focus on long-term cardiovascular outcome studies to definitively establish whether the blood pressure benefits observed translate into reduced cardiovascular events, stroke, and renal disease progression. Additionally, investigation of optimal patient phenotypes most likely to benefit from this combination approach would facilitate personalized treatment strategies. The integration of novel antihypertensive combinations into clinical practice guidelines requires ongoing evaluation through well-designed clinical trials with robust methodology and adequate follow-up duration.

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Conflicts of interest: There are no conflicts of interest.

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