CONTROL

Efficacy of Noninvasive Hemodynamic Monitoring to Target Reduction of Blood Pressure Levels (The CONTROL Trial)

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Background

Hypertension is a hemodynamic disorder, as blood pressure (BP) rises as the result of higher cardiac output, systemic vascular resistance, or both combined. Antihypertensive therapy guided by noninvasive hemodynamic monitoring with impedance cardiography (ICG) has demonstrated improved BP control in resistant hypertension treated by specialists.

We hypothesized that hypertension therapy guided by hemodynamic monitoring with ICG could aid Physicians in reducing BP more effectively than standard care in a population of uncontrolled hypertensive patients receiving one or more medications at a primary care setting.

Methods

Eligibility: Male and female patients between 18 and 75 were eligible if they had a diagnosis of essential hypertension and were currently on one but less than four antihypertensive medications with ranges of systolic BP of 140 to 179 mm Hg and/or diastolic BP of 90 to 109 mm Hg using JNC-VI criteria.

Treatment Assignment: Eligible patients (N=164) underwent a two-week washout period during which time all antihypertensive medications were discontinued according to manufacturer's recommendations. After the two-week washout period, patients meeting inclusion/exclusion criteria were randomized in a 3:2 ratio to standard antihypertensive therapy per JNC-VI hypertension guidelines (Standard Care Arm, N=95) or antihypertensive therapy aided by ICG hemodynamic information (Hemodynamic Care Arm, N=69). After screening and medication washout, each patient was seen in the office monthly for a total of three months.

Procedures: All BP determinations were made in the seated position using the oscillometric technique. ICG data was collected by a trained technician at each visit in all patients, but were not revealed to clinicians in the Standard Care Arm. ICG was performed using a commercially available device (BioZ® ICG Monitor, CardioDynamics, San Diego, CA).

Outcome Measures: The primary endpoints for the study were the reductions in systolic and diastolic BP from baseline and post-washout visits. The secondary endpoints for the study were the percentage of patients achieving goal BP (<140/90 mm Hg) and aggressive goal BP (<130/85 mm Hg), and the percent of patients reaching goal BP (<140/90 mm Hg) with cardiac index and systemic vascular resistance index in the normal range.

Interventions: In the Standard Care Arm, medication choices were made at the discretion of the physician investigator consistent with published guidelines, usual practice patterns, and patient clinical characteristics. In the Hemodynamic Care Arm, the treating physician was encouraged to use the hemodynamic data to guide therapeutic decisions about pharmacologic agents, dosing, and instructional guidance to the patient. When systemic vascular resistance index was elevated and cardiac index was low or normal, initiation or intensification of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, or vasodilator drugs were suggested. When cardiac index was high and systemic vascular resistance index was normal or low, initiation or intensification of a beta blocker or central acting agent was suggested. In addition, changes in the patient's fluid status were evaluated with the thoracic fluid content parameter at each visit to aid titration of diuretic dosages.

Statistical Analysis: Continuous variables are expressed as mean ± standard deviation and categorical variables as N (%). Differences in continuous variables between treatment groups were examined with t-tests and by analysis of variance. Discrete variables were compared using Fisher's exact tests. Defined daily doses for each class of dedication were calculated using established WHO criteria.

Results

A total of eleven primary care centers participated in the study between November 2002 and November 2004. Of 262 patients screened, 184 meeting the inclusion criteria were randomized into the study. A total of 164 patients (95 in the Standard Care Arm and 69 in the Hemodynamic Care Arm) completed the study and were analyzed.

There were no significant differences in patient demographic, clinical, BP, number of medications, or ICG-determined variables at baseline (Table 1).

As shown in Table 2, systolic BP reductions in the Hemodynamic Care Arm were greater from baseline (19 ± 17 vs. 11 ± 18 mm Hg, $p<0.01$) and post-washout visit (25 ± 18 vs. 19 ± 17 mm Hg, $p<0.05$) than in the Standard Care Arm.

Diastolic BP reductions were also greater in the Hemodynamic Care Arm from baseline (12 ± 11 vs. 5 ± 12 mm Hg, $p<0.001$) and post-washout (17 ± 12 vs. 10 ± 11 mm Hg, $p<0.001$) than in the Standard Care Arm. As shown in Figure 1, goal BP (< 140/90 mm Hg) was achieved more frequently in the Hemodynamic Care Arm than in the Standard Care Arm (77 vs. 57%, $p<0.01$).

Similarly, the aggressive goal BP (< 130/85 mm Hg) was also achieved with greater frequency (55 vs. 27%, $p<0.0001$). Patients in the Hemodynamic Care Arm had a greater drop in systemic vascular resistance index (SVRI) from baseline (433 ± 661 vs. 219 ± 667 dyne sec m^2 cm^{-5}, $p<0.05$) and post-washout (599 ± 739 vs. 369 ± 642 dyne sec m^2 cm^{-5}, $p<0.05$). The percentage of patients achieving normal hemodynamic values, defined as normal values of blood pressure with simultaneously normal cardiac index and systemic vascular resistance index, was 52% in the Hemodynamic Care Arm and 29% in the Standard Care group ($p < 0.01$).

At the final visit, patients in the Standard Care Arm were on 2.0 ± 0.8 medications compared to 2.1 ± 0.9 for the Hemodynamic Care Arm ($p > 0.05$). There were no differences in the number of patients prescribed ACE inhibitors, beta blockers, or calcium channel blockers between the two Arms. In the Hemodynamic Care Arm, the use of angiotensin II receptor blockers was higher (46.4% vs. 30.5%, $p<0.05$). However, the number of patients in the Hemodynamic Care Arm vs. the Standard Care Arm who were prescribed either an ACE inhibitor or angiotensin II receptor blocker did not reach significance (87.0% vs. 76.8%, $p>0.05$).

Table 1. Baseline Characteristics

	Standard Care N=95	Hemodynamic Care N=69	P Value
Age (y)	54.5 ± 9.4	55.2 ± 9.2	ns
Body mass index (kg/m^2)	30.2 ± 6.3	30.8 ± 5.1	ns
Male	51 (53.4)	38 (55.1)	ns
Ethnicity			
White, non-Hispanic	75 (79.0)	53 (76.8)	ns
White, Hispanic	7 (7.4)	5 (7.3)	ns
Black	8 (8.4)	6 (8.7)	ns
Asian	3 (3.2)	3 (4.4)	ns
History			
Type II diabetes mellitus	4 (4.2)	3 (4.4)	ns
Ischemic heart disease	2 (2.1)	5 (7.3)	ns
Hyperlipidemia	14 (14.7)	12 (17.4)	ns
Blood pressure and hemodynamics			
Systolic BP (mm Hg)	147 ± 9	148 ± 12	ns
Diastolic BP (mm Hg)	87 ± 10	89 ± 8	ns
Heart rate (bpm)	75 ± 12	74 ± 13	ns
Cardiac index (L/min/m^2)	2.8 ± 0.5	2.9 ± 0.6	ns
Systemic vascular resistance index (dyne sec cm^{-5} m^2)	2933 ± 576	2956 ± 605	ns
Thoracic fluid content (/kOhm)	28.6 ± 4.9	28.0 ± 4.8	ns
Medications			
Total antihypertensive medications	1.7 ± 0.8	1.7 ± 0.7	ns

Categorical variables are expressed as N (%), continuous variables as mean ± SD; ns, not significant.

At the final visit, patients who were prescribed diuretics in the Standard Care Arm were on a higher dose compared to those so prescribed in the Hemodynamic Care Arm (17.6 ± 8.4 vs. 12.2 ± 2.0 mg/day, $p<0.01$). There were no differences in the percent of patients in the Hemodynamic Care vs. Standard Care Arm on one (25% vs. 26%), two (48% vs. 53%), three (19% vs. 15%), four (9% vs. 5%), or five (0% vs. 1%) antihypertensive medications at the final visit. After each study visit in which antihypertensive medications were prescribed, there were no differences in patient-reported compliance with antihypertensive medications.

Table 2. Final Blood Pressure and Hemodynamic Values

	Standard Care N=95	Hemodynamic Care N=69	P Value
Systolic blood pressure (mm Hg)			
Final	136 ± 15	129 ± 14	<0.01
Δ Baseline to Final	-11 ± 18	-19 ± 17	<0.01
Δ Post-washout to Final	-19 ± 17	-25 ± 18	<0.05
Diastolic blood pressure (mm Hg)			
Final	82 ± 10	76 ± 11	<0.01
Δ Baseline to Final	-5 ± 12	-12 ± 11	<0.001
Δ Post-washout to Final	-10 ± 11	-17 ± 12	<0.001
Heart rate (beats per minute)			
Final	77 ± 13	76 ± 11	ns
Δ Baseline to Final	1 ± 12	2 ± 13	ns
Δ Post-washout to Final	-2 ± 13	-2 ± 13	ns
Cardiac index (l/min/m^2)			
Final	2.9 ± 0.5	2.9 ± 0.5	ns
Δ Baseline to Final	0.1 ± 0.5	0.0 ± 0.5	ns
Δ Post-washout to Final	0.0 ± 0.5	0.0 ± 0.5	ns
Systemic vascular resistance index (dyne sec cm^{-5} m^2)			
Final	2714 ± 619	2523 ± 581	<0.05
Δ Baseline to Final	-219 ± 667	-433 ± 660	<0.05
Δ Post-washout to Final	-369 ± 642	-599 ± 738	<0.05
Thoracic fluid content (/kOhm)			
Final	27.8 ± 4.1	28.2 ± 4.9	ns
Δ Baseline to Final	-0.8 ± 3.6	0.1 ± 3.0	ns
Δ Post-washout to Final	-1.2 ± 3.3	-0.2 ± 2.7	<0.05

Variables are expressed as mean ± SD; ns, not significant.

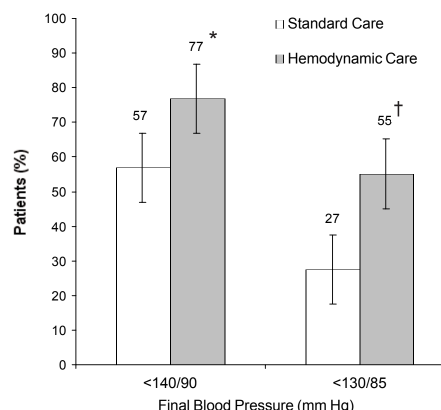

Figure 1. Comparison of Standard Care and Hemodynamic Care Arms for target blood pressure achievement; shown with 95% confidence intervals; * = $p<0.01$ vs. Standard Care, † = <0.0001 vs. Standard Care.

Conclusion

The results of this study indicate that antihypertensive therapy guided by ICG hemodynamic measurements in uncontrolled hypertension on one or more antihypertensive medications is more effective than standard care. This was evident by greater reductions in systolic and diastolic BP and by achieving a better level of BP control. Our study showed that in clinical practice, inclusion of ICG hemodynamic assessment may improve BP control rates in patients who are not controlled on initial therapy.