Control of Moderately Raised Blood Pressure

Report of a Co-operative Randomized Controlled Trial

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Summary

A study was designed to investigate the effect on morbidity and mortality of lowering diastolic blood pressure levels of between 100 and 120 mm Hg to below 100 mm Hg. Fifty-eight men and women, aged from 45-69 years, with blood pressure levels between 100 and 120 mm Hg were matched for age, sex, and blood pressure levels with 58 control patients. The maintenance of diastolic blood pressures at levels below 100 mm Hg was successfully carried out without serious drug side effects. Treatment effectively maintained diastolic pressures below 100 mm Hg, but no effect was shown on other terminating events. Few problems were found in the management of patients with minimally raised blood pressure, most of whom were symptom-free. The treatment and control groups became less comparable as increasing numbers of patients in the control group were withdrawn from the trial as diastolic pressures rose above 130 mm Hg.

Introduction

The benefits of hypotensive treatment for patients with malignant hypertension or severe essential hypertension are now established (Dustan *et al.*, 1958; Harington *et al.*, 1959; Smirk, 1961; Lee *et al.*, 1963; Marshall, 1964; Leishman and Sandler, 1965).

In patients with less severe hypertension the benefits of treatment are not so clear cut. Three randomized controlled trials have shown some reduction in morbidity and mortality from cardiovascular disease as a result of hypotensive treatment (Hamilton *et al.*, 1964; Wolff and Lindeman, 1966; Veterans' Administration Co-operative Study Group, 1967, 1970). However, these trials have limitations and their results need to be interpreted with some caution. In the study by Hamilton and his co-workers all the patients were symptom-free, but the distribution of diastolic pressures on entry to the trial ranged from 110 to 170 mm Hg and only a small proportion had diastolic pressures between 110 and 120 mm Hg. In Wolff and Lindeman's investigation 38% of the patients already showed evidence of target organ involvement, 80% were on hypotensive treatment when they were admitted to the trial, and only 48 of the 87 taking part completed the trial. All patients investigated by the Veterans' Administration Co-operative Study Group were male. Their initial diastolic blood pressures of 115-129 mm Hg (1967 report) and 90-114 mm Hg (1970 report) were average blood pressures during the fourth day of admission to hospital, and they were highly selected with respect to co-operation and regular consumption of medication. These excellent trials showed a significant reduction of cardiovascular incidents in the treated groups but the limitations mentioned above made conclusions of uncertain general application.

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Aims and Methods

The present study was designed to test the hypothesis that treatment reduces morbidity and mortality from cardiovascular diseases in a group of patients with initial diastolic pressures between 100 and 120 mm Hg. We also studied the incidence of side effects from drugs used in the treatment, and observed the willingness of all the patients, most of whom were free of symptoms attributable to raised blood pressure, to continue taking drugs for any length of time.

The study was carried out in Cardiff and London and in both centres the population was drawn from two sources: surveys of random samples of the general population and hospital patients.

The study ran in both centres from July 1967 to December 1970 and was continued for a further year in St. Thomas's Hospital. The criteria for selection were that those studied should be men and women between the ages of 45-69 years with two casual, sitting diastolic blood pressures of between 100 and 120 mm Hg on each of two occasions separated by an interval of at least two weeks. The blood pressure throughout the trial was recorded by a Garrow random-zero sphygmomanometer (Wright and Dore, 1970) after the patients had been sitting quietly for five minutes. The patients selected had to be willing to join the trial and attend a clinic regularly. Patients were excluded if: (*a*) there was evidence of renal or cardiac failure or papilloedema; (*b*) there was a history of cerebrovascular accident or myocardial infarct within the preceding three months; (*c*) any serious or potentially fatal disease or disability was present that would prevent regular attendances or which contraindicated hypotensive therapy; (*d*) they were currently receiving antihypertensive therapy; or (*e*) there was evidence that hypertension was secondary to a surgically remediable condition.

The patients were allocated at random to either the control or treatment group. The series was balanced for age and sex after every 10 allocations. The untreated control group received calcium lactate tablets. Those in the treatment group were treated with any combination of bendrofluazide with potassium supplement, methyldopa, or debrisoquine, the choice of treatment being at the discretion of the physician. The aim of treatment was to reduce the diastolic blood pressure below 100 mm Hg as far as was consistent with the patient's comfort. Progression from one regimen to the next depended on the blood pressure response and incidence of side effects. Reasons for withdrawal from the trial were death, persistent poor attendance, or poor co-operation for either social or medical reasons, and in the control group a rise of diastolic pressure above 130 mm Hg on one occasion or other clear indications for antihypertensive treatment. The physicians knew which treatment the patient was being given, but the random zero sphygmomanometer (Wright and Dore, 1970) eliminated bias in measurement. If the diastolic blood pressure rose to 130 mm Hg or over in a patient in the control group the patient was immediately withdrawn from the trial and given hypotensive treatment.

Before patients were admitted to the trial the following

investigations were carried out: haemoglobin, packed cell volume, cholesterol, random blood glucose, uric acid, sodium, potassium, bicarbonate, urinary vanillylmandelic acid, blood urea, serum calcium, serum creatinine, E.C.G., chest *x*-ray examination, intravenous pyelogram, renogram, and the urine was tested for albumin and sugar and a clean catch was cultured. These examinations were repeated every six months with the exceptions of the intravenous pyelogram and renogram. The patients were seen at a minimum interval of three months. At one of the centres patients were seen routinely every six weeks either at a clinic or at home.

Results

The patients in the control and treatment groups were compared for age, weight, the levels of blood glucose, and blood urea at the time of entry to the trial (table I). E.C.G. tracings were recorded on 101 of the 116 patients, and have been classified using the Minnesota code. One patient in each group showed E.C.G. evidence of left ventricular strain and hypertrophy. None showed evidence of probable coronary disease (Higgins *et al.*, 1965). Six women in the control group and two patients in each of the other three groups showed evidence of possible coronary disease. Two men in the control group showed T-wave inversion only.

TABLE I—*Patients Admitted to Trial*

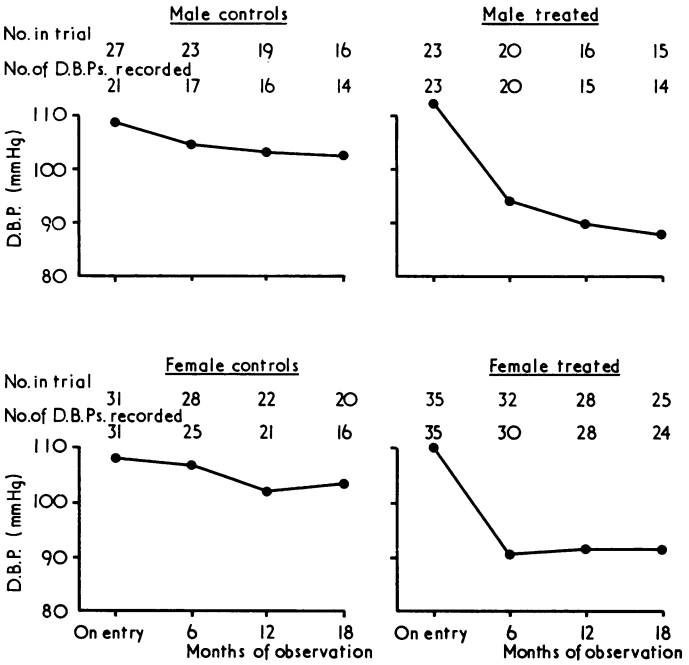
Group	No. of Patients	Source		Mean Age	Mean Weight (kg)	Mean Blood Urea (mg/100 ml)	Mean Months in Trial
		Survey	Other				
Men:							
Controls ..	27	7	20	55·2	78·3	30	21·6
Treated ..	23	4	19	54·4	80·6	36	22·4
Women:							
Controls ..	31	9	22	56·5	69·7	29	24·3
Treated ..	35	13	22	55·7	66·1	29	26·9

Seventy-eight patients had intravenous pyelograms, 53 had renograms, and 18 had neither investigation. Eleven abnormalities were shown by intravenous pyelogram, six in the treated group and five in the controls; in the main these were minor anatomical abnormalities. No patient was excluded from the trial because of the findings.

The diastolic blood pressure levels are shown in the figure. They have been presented as those pressures observed in patients at six-monthly intervals from their time of entry to the trial—the length of time patients stayed in the trial varied from one month to four years. Both the numbers of patients who should have attended the clinics and the number of those who actually attended and in whom blood pressure measurements were made are given. For the treatment groups these numbers are very similar, though 100% attendance was not always achieved. In the controls the situation was less satisfactory as attendance was never complete on any occasion.

The mean levels of blood pressure in the treated groups fell in the first six months and this fall was maintained. In the controls levels remained around the mean on entry for 18 months. By this time six of the nine controls whose diastolic pressures rose above 130 mm Hg had been withdrawn from the trial and so the blood pressure levels in the two groups were no longer comparable.

The treatment group contained 58 patients; 31 were treated with bendrofluazide with potassium, four with methyldopa alone, 12 with methyldopa and bendrofluazide, and 11 with debrisoquine with bendrofluazide. No patient had to be withdrawn from the trial as a result of drug side effects but two refused to continue drug taking.



Mean diastolic blood pressure (D.B.P.) levels at six-monthly intervals.

Seventeen patients were withdrawn from the trial for medical reasons (table II), 14 in the control and three in the treated group. Nine of the controls left because the diastolic pressures rose above 130 mm Hg, two died, two developed a myocardial infarct and one cardiac failure, in comparison with three in the treated group, one of whom died, one was admitted to a geriatric hospital, and one developed a myocardial infarct.

TABLE II—*Medical Indications for Leaving Trial*

Group	Indication	No. of Patients	Total
Controls:			
Men ..	Diastolic blood pressure rose above 130 mm Hg	5	8
	Died—cause unknown	2	
	Myocardial infarct and pulmonary embolus ..	1	
Women	Diastolic blood pressure rose above 130 mm Hg	4	6
	Died infarct of cardiac septum	1	
	Developed cardiac failure	1	
Treated:			
Men ..	Admitted to geriatric hospital—senility ..	1	1
Women..	Died of fractured skull	1	2
	Myocardial infarct	1	

The 19 who left for non-medical reasons either defaulted or were uncooperative and of these 10 left the trial within a year of entry. The patients had initially been drawn from two sources, those found on screening a random sample of the population and those referred from hospital. Ten of the 16 who left the trial came from the survey population, six from the hospitals. The mean diastolic pressures of all patients entering, remaining, and withdrawn from the trial for either medical or management reasons are summarized in table III.

Discussion

This trial has not provided evidence that treatment of moderately severe hypertension reduces the likelihood of cardiovascular accidents, but this does not mean that the hypothesis is incorrect. It is possible, in retrospect, to define several ways in which the trial was unsatisfactory; some of these deficiencies were in the design of the trial, and others are inherent in any attempt to influence prospective illness in asymptomatic people.

TABLE III—*Mean Diastolic Pressures during Trial. Figures in Parentheses are Numbers in each Group*

Group	On Entry	Remained in Trial	Left for Medical Reasons	Left for Management Reasons	Left Area
Controls:					
Men	109 (27)	103 (13)	124 (8)	96 (5)	96 (1)
Women	109 (31)	105 (20)	129 (6)	96 (4)	90 (1)
Total ..	109 (58)	104 (33)	126 (14)	96 (9)	93 (2)
Treated:					
Men	112 (23)	91 (15)	100 (1)	99 (6)	103 (1)
Women	110 (35)	89 (29)	99 (2)	84 (4)	—
Total ..	110 (58)	90 (44)	100 (3)	92 (10)	103 (1)

One design defect, which resulted in the exclusion of a large number of patients from the trial, was the requirement that two separate measurements of diastolic blood pressure should lie between 100 and 120 mm Hg. These are relatively narrow limits, and commonly the second measurement lay just below 100 mm Hg. This phenomenon has been noted by Dunne (1969) and Hart (1970).

In retrospect, it was probably unnecessary to carry out intravenous pyelography or renography. Several patients found pyelography unpleasant, and in some cases their subsequent management on admission to the trial was difficult. The yield from this investigation was small and of little relevance. These findings agree with those of Gifford (1969) who reported that 4·5% of 5,000 patients with hypertension had evidence of renovascular disease, but only 0·13% were treated surgically.

The other investigations carried out before admission to the trial were necessary to determine comparability of the control and treated groups and to establish a baseline so that the incidence of complications could be established.

We found that 31 of the 58 patients in the treatment group had their blood pressure levels maintained at 100 mm Hg or less by bendrofluazide without the addition of any hypotensive drugs. The drug side effects were minimal, and did not result in any patient leaving the trial. The maintenance of diastolic pressure below 100 mm Hg presented few problems. The mean levels of diastolic pressure of those in the treatment group were found to be consistently lower than those of the controls. This was both surprising and gratifying as the difficulty in persuading symptom-free patients to take drugs for any length of time is well known (Fox, 1962).

Whether similar results would be obtained in a busy general practice when such patients would no longer be identified as a special group and cared for in a clinic designed to meet their needs has still to be established. To persuade people who are symptom-free to continue taking tablets for any length of time demands a high level of commitment on the part of the practitioner. As Caldwell and others (1970) observed, the physician is the most important influence in keeping such a patient on treatment.

The main difficulty in interpreting the results of this trial lies in the disappearance of increasing numbers of patients from the control group due to diastolic pressures rising above 130 mm Hg. We accepted a single diastolic blood pressure reading of over 130 mm Hg as an indication for removal from the trial and institution of active treatment because it was felt to be unethical to allow patients to continue with blood pressures at this level. It might have been better to require more than one measurement of blood pressure above this level. If withdrawal because of rising blood pressure is regarded as a unsatisfactory outcome then there were many more of these cases in the control than the treated group, but we are doubtful of the validity of this interpretation. Another consequence of these withdrawals is to alter the comparability of the groups. However comparable the two groups may have been at the outset, within 18 months this comparability had disappeared. In the present series the main function of treatment seems to be to prevent the rise of blood pressure, but it cannot be concluded from this evidence that treatment effectively reduces the risks of death or morbid events due to cardiovascular disease. One possible solution might be to maintain the diastolic pressures of the patients in the control group between 110 and 120 mm Hg, or whatever upper limit of diastolic pressure was considered acceptable and compare the deaths and morbid events in this group with those in whom the pressure is maintained below 100 mm Hg. One thing is clear—the controls must be watched as cartfully and as often as the treated patients. "In any comparison both groups are of equal and fundamental importance; there can be no glossing over the nature of the control" (Hill, 1962).

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