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Blood pressure reduction in the elderly: a randomised controlled trial of methyldopa

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Abstract

A total of 123 out of 549 elderly residents of local authority welfare homes in Nottinghamshire were found at screening to have a standing or lying diastolic blood pressure of 100 mm Hg or more. These 123 subjects were randomly allocated to simple observation or to treatment with methyldopa. The cumulative mortality was similar in the observed and treated groups and in the normotensive group from which the subjects had been separated.

Thus moderate hypertension, whether treated or not, was not a major risk predictor in the elderly population studied.

Introduction

Heart disease and stroke account for most deaths in people over 65 years of age.¹ Systemic arterial blood pressure is a major risk predictor for cardiovascular disease and cerebrovascular disease in younger groups, and there is clear evidence that hypotensive treatment can reduce mortality and morbidity,² but only 10% of the patients included in 41 published trials of hypotensive treatment were aged over 60.³ We therefore carried out a simple prospective study of mortality in elderly hypertensive patients randomly allocated to treated and observed groups. We also recorded the survival of elderly subjects not entered in our trial, and this allowed us to determine the predictive power of systemic blood pressure in an elderly population.

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Patients and methods

We initially intended to identify patients with diastolic pressures over 100 mm Hg from consecutive new admissions to the two active geriatric hospitals in Nottingham. Altogether 429 patients were screened, but it soon became clear that many of them were already disabled by strokes and other major vascular disorders. We feared that this would give too high a proportion with end-stage disease for our objectives to be achieved. We then turned to the population resident in the local authority welfare homes run by Nottinghamshire County Council. Nine homes within easy travelling distance of the Nottingham hospitals were identified and the general practitioners caring for the residents approached. The practitioners at two of the homes were unwilling for their patients to be included, so we therefore approached the matrons and residents of the remaining seven homes. The entry criteria, treatment, follow-up, and endpoints used were kept simple, and the plan was to analyse outcome purely in terms of mortality on an intention-to-treat basis by comparing the survival patterns in subjects initially allocated to the observed and treated groups.

Recruitment—One of us (MES) visited the homes in turn during a two-year period, approached the residents, explained the purpose of the study, and ascertained their willingness to take part. Systemic blood pressure was then measured with a normal sphygmomanometer, using either arm, with the subject supine and standing. Phase IV (muffling) was taken as the diastolic endpoint and was recorded to the nearest 5 mm Hg. Systolic pressures were recorded to the nearest 10 mm Hg. Any subject with a single casual diastolic pressure of 100 mm Hg or more was considered for the study. The highest diastolic pressure encountered was 145 mm Hg, which was recorded in four subjects. Three of these subjects were randomised to the observed group, from which one was at once withdrawn to be treated by the attending practitioner. The others remained in the trial.

Pre-entry examination was confined to seeking a history or physical signs of heart failure or stroke. No conditions incompatible with hypotensive treatment were found. No routine investigations were performed.

Randomisation—To avoid seasonal and interhome bias, because entry to the trial occurred over a two-year period, a block of 24 sealed envelopes was prepared for each of the seven homes. Each envelope contained a randomly generated instruction to "observe" or to "treat." The computer program used had instructions to truncate runs of consecutive assignments longer than four. After a resident had been found eligible for the study and a case record completed the next envelope in the sequence for that home was opened and the regimen therein followed.

Regimens—The observed subjects received no medication over and above any treatment that their general practitioner deemed to be

necessary for other aspects of their health. The practitioners were asked not to prescribe specific hypotensive agents without withdrawing their patients from the trial. Of the hypotensive agents in general use when the trial was begun (1972), we opted to use methyldopa in an initial dose of 250 mg twice daily, which was subsequently adjusted as necessary to bring the standing diastolic pressure towards the target of 90 mm Hg. The homes were visited at intervals between 1972 and 1976 by MES. At each visit the state of the trial recruits was ascertained (dead, admitted to hospital, or still in residence). Those still in residence were re-examined and their blood pressures checked, any morbidity or side effects recorded, and their treatment adjusted.

Results

COMPARABILITY OF RANDOMISED GROUPS

Altogether 549 residents were screened, of whom 123 qualified for entry to the trial on grounds of diastolic blood pressure. One was withdrawn from the observed group as noted above, and two were lost to follow-up, one from each group. Of the 120 subjects remaining, 60 were randomised to the treated and 60 to the observed group. Table I shows the age and sex of the groups, table II their existing morbidity and treatment, and table III their blood pressures on entry to the trial. Table I also gives details of the residents who did not qualify for entry because their casual diastolic blood pressure was below 100 mm Hg ("normotensive" subjects).

Tables I-III show that the groups were well matched for age, sex, pre-existing disease, and blood pressures on entry. None of the differences was significant, and the only two that approached significance were that the treated patients were younger and had lower mean standing systolic pressures. This would have been expected to favour survival in the treated rather than the observed group.

CHANGE IN BLOOD PRESSURE

The blood pressures recorded at the first routine visit after six months from entry to the trial were available in 36 surviving treated patients and 39 surviving observed patients. These were compared

with each patient's blood pressure on entry, and table IV shows the mean changes.

The mean blood pressure fell in both groups after entry, as has been observed in many other longitudinal studies³; this was due to a regression towards the mean of a group selected because they possessed a high level of a variable characteristic. As these were direct longitudinal comparisons the reductions in blood pressure in table IV do not merely reflect a higher death rate in those with higher blood pressures on entry. On the contrary, the mean pressures on entry in those in whom no six-month record was available were slightly but not significantly lower than those shown in the table.

TABLE IV—Change in blood pressure (mm Hg) six months or more after entry to trial

	Treated group (n = 36)		Observed group (n = 39)		p for difference*
	Mean change	SEM	Mean change	SEM	
Standing systolic	.. -21.5	5.28	-3.1	3.56	0.008
Standing diastolic	.. -11.0	2.62	-3.2	2.40	0.02
Lying systolic	.. -18.9	4.92	-6.5	3.47	0.04
Lying diastolic	.. -9.9	2.47	-5.7	3.18	0.04

*Two-tailed probability (Mann-Whitney test) that differences between changes in blood pressure in treated and observed groups are attributable to chance alone.

EFFECT ON OUTCOME

Survival data were available for every participant in the trial except for the three already mentioned. Not all members of the treated group, however, continued active treatment for the rest of their lives: nine stopped treatment because of side effects (sleepiness, fatigue, confusion, and postural syncope).

Table V shows survival calculated by the life-table method⁶ at various times after entry in the treated and observed groups of hypertensive subjects and in the normotensive group from which they had been separated. Because this was an intention-to-treat study survival was not adjusted for withdrawals from treatment; three members of the observed group who had survived three, 26, and 29 months and died in a fire were treated as withdrawals. The log-rank test was used to compare the survival of the groups; this gives a test statistic analogous to χ^2 for the cumulative deaths in each group compared with the exposure to the risk of death calculated by apportioning the total deaths to each group according to its current size.⁶ There were no significant differences between the groups, although survival was highest in the untreated hypertensive group and lowest in the treated group at many of the time intervals after randomisation.

TABLE V—Percentage of subjects surviving in each group calculated by life-table method

Months from entry	Hypertensive		Normotensive	Probability that groups differ by chance alone (log rank test)*
	Treated	Observed		
1	96.7	98.3	98.4	0.8 < p < 0.9
3	86.6	91.6	92.9	0.8 < p < 0.9
6	78.3	89.9	84.7	0.2 < p < 0.3
12	66.7	79.7	74.6	0.2 < p < 0.3
18	58.3	71.2	62.0	0.2 < p < 0.3
24	53.3	54.3	52.1	0.7 < p < 0.8
36	35.0	39.9	38.1	0.5 < p < 0.7
48	21.5	28.6	27.5	0.3 < p < 0.5
60	19.3	26.3	18.6	0.3 < p < 0.5
90	10.3	9.9	12.4	0.5 < p < 0.7

We recorded morbidity, as well as mortality, by noting whether subjects required transferring from their residential home to hospital during the observation period. Six patients in the observed and four in the treated group developed non-fatal cardiovascular events as defined by the occurrence of myocardial infarction, stroke, or heart failure or the deterioration of pre-existing heart failure. This low ratio of morbidity to mortality initially surprised us until we realised that it applies to many other clinical conditions in groups with a mean age of 80, in which high case-fatality rates from myocardial infarction, pneumonia, and uncomplicated operations have been described.

TABLE I—Composition of groups by age and sex

	n	Mean age (years)	SD	Age (years)				
				< 65	65-74	75-84	85-94	≥ 95
Observed group:								
Men ..	15	81.4	12.98	2	2	4	6	1
Women ..	45	81.2	7.72	2	6	21	16	
Treated group:								
Men ..	16	79.9	7.25		4	8	4	
Women ..	44	79.8	7.49		10	22	12	
Normotensive subjects:								
Men ..	128	81.0	8.06	4	22	60	39	3
Women ..	298	83.1	7.44	6	37	111	135	9

TABLE II—State of patients on entry to trial

	Cerebro-vascular disease	Cardio-vascular disease	Cerebro-vascular and cardio-vascular disease	Previously taking hypo- tensive drugs	Other drugs
Observed group	6	7	2	1	5
Treated group	8	2	1	5	10

TABLE III—Blood pressure (mm Hg) on entry to trial

	Treated group			Observed group			p for difference*
	n	mean	SEM	n	mean	SEM	
Standing systolic	59	190.1	3.04	58	197.7	3.45	0.06
Standing diastolic	59	106.7	1.32	58	108.5	1.78	0.41
Lying systolic	60	198.8	3.38	60	202.6	3.48	0.23
Lying diastolic	60	105.9	1.69	60	108.5	1.96	0.24

*These values were computed by applying the Mann-Whitney test to large groups⁴ and are two-tailed probabilities that the groups differ only randomly in their rank sums.

Discussion

Treatment for hypertension is one of the commonest causes of drug-induced illness in the elderly, so "treatment should be started only in the presence of well-defined and justifiable indications."⁷ There is, however, no generally agreed definition of either "the elderly" as a group or "hypertension" in this age group, and many clinicians are hoping that clarification will come from the current trial of the European Working Party on Hypertension in the Elderly (EWPHE), of which preliminary reports⁸⁻⁹ have been published.

The proportion of elderly subjects in trials so far completed has been low. For example, in the pioneering Veterans Administration study¹⁰ only one in five of the subjects was over 60, while in the Hypertension Detection and Follow-up Program¹¹ and the Australian national blood pressure study¹² the upper age limit was 69. The age group 60-69 therefore contributed only 22% and 17% respectively of these study populations.

In 1973 the EWPHE was set up to remedy this major gap in our knowledge.⁸⁻⁹ Some 600 patients aged over 60 with hypertension have been allocated to two groups in the multicentre trial; one group receives placebo tablets while the other receives a thiazide diuretic plus triamterene, methyldopa being added if adequate reduction in blood pressure is not achieved. Preliminary results show that the pressures in the treated group have been reduced by 25 mm systolic and 10 mm diastolic, which is similar to the reduction in pressure produced by methyldopa in our more limited study. As in our study, recruitment to the EWPHE took place over a period and it was decided that results on morbidity and mortality should not be published until all the entrants had been followed up for an adequate time. If the active treatment regimen was found to produce harm or appreciable benefit, however, then the trial would be terminated. As this has not happened it has been inferred that "the substantial fall in blood pressure has not as yet been accompanied by a statistically significant reduction in stroke, myocardial infarction, and death."⁷

Our study was unusual in several ways: all the observations were made by one doctor, and the study was concerned exclusively with elderly subjects, 83% of whom were over 74. They were generally mobile but were living under conditions in which treatment could be supervised by the matron of the home, and in a subsequent report we shall be comparing their survival patterns with those of people living in the community. The observed and treated groups were well matched in numbers, distribution between the sexes, previous health, and previous medical treatments. The modest differences in age distribution and blood pressure on entry (of which only the difference in standing systolic pressure approached significance) should have favoured survival in the treated group. Under these circumstances our finding that treatment is highly unlikely to be associated with increased survival is particularly clear cut. The strictures of Freiman *et al.*¹³ against excessive readiness to accept the null hypothesis were based on much narrower failures to reach significance than ours.

The disadvantages of our study are its comparatively small scale and that it was not placebo controlled in a double-blind protocol, whereas the EWPHE trial is five times larger and is placebo controlled. The thiazide component of the EWPHE regimen may contribute to inconclusive results by its ability to increase risk factors such as glucose intolerance,⁹ hyperuricaemia, and hyperreninaemia¹⁴ as well as to reduce blood pressure. That this may not be a purely theoretical concept is suggested by a trial carried out in elderly men¹⁵ in which mortality was increased in a thiazide-treated group. Moreover, in that study, as in ours, not only was there no improvement in survival with treatment but blood pressure on entry did not correlate with outcome.

Our study shows the difficulty of identifying an appropriate group in whom to conduct an intervention trial. A parallel may be drawn with the problem of pulmonary embolisation¹⁶: if a group is chosen in whom the risk of embolisation is almost

universal, such as elderly patients with hip fractures, enough embolic events will occur in a fairly small trial to permit ready detection of a therapeutic effect on the event itself. If, however, non-embolic deaths are also common in the group total mortality will be little changed. On the other hand, in younger patients undergoing general surgery mortality is low but pulmonary embolism makes a major contribution to it. In such patients a large trial would be needed to show a beneficial effect of treatment. Between these extremes must lie the most appropriate group for study—namely, one in which the modifiable process occurs with sufficient frequency to contribute to death and in which death is not often due to other causes. The inherent difficulty in identifying such a group has necessitated large-scale trials in hypertension in younger subjects.¹⁷

In our trial neither hypertension nor its treatment was shown to be associated with altered survival. This must cast doubt on the assumptions that the implications of hypertension in the elderly are the same as in younger groups and that hypertension in the elderly should be treated.¹⁸ In the light of our findings and of the discomfort and morbidity associated with hypotensive treatment we should not embark on such treatment in this age group until evidence of benefit is adduced from further trials using other hypotensive agents.

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References

- O'Malley K, O'Brien E. Management of hypertension in the elderly. *N Engl J Med* 1980;**302**:1397-401.
- Anonymous. Mild hypertension. *Br Med J* 1980;**280**:1062-3.
- Koch-Weser J. Arterial hypertension in old age. *Herz* 1978;**3**:235-44.
- Siegel S. *Non-parametric statistics for the behavioural sciences*. International student ed. Tokyo: McGraw-Hill Kogakusha, 1956:120-7.
- Gardner MJ, Heady JA. Some effects of within-person variability on epidemiological studies. *J Chronic Dis* 1973;**26**:781-95.
- Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;**35**:1-39.
- Anonymous. Antihypertensive treatment in the elderly. *Br Med J* 1979;ii:1456-7.
- Amery A, Berthaux P, Birkenhager W, *et al.* Antihypertensive therapy in patients above age 60 years (fourth interim report of the European Working Party on High Blood Pressure in the Elderly: EWPHE). *Clin Sci Mol Med* 1978;**55**:263-70S.
- Amery A, Berthaux P, Bulpitt C, *et al.* Glucose intolerance during diuretic therapy: results of trial by the European Working Party on Hypertension in the Elderly. *Lancet* 1978;ii:681-3.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. III. Influence of age, diastolic pressure and prior cardiovascular disease; further analysis of side effects. *Circulation* 1972;**32**:499-510.
- Hypertension Detection and Follow-up Program Cooperative Group. Patient participation in a hypertension control program. *JAMA* 1978;**239**:1507-14.
- Management committee. Report. The Australian therapeutic trial in mild hypertension. *Lancet* 1980;ii:1261-7.
- Freiman JA, Chalmers TC, Smith H Jr, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomised control trial. Survey of 71 "negative" trials. *N Engl J Med* 1977;**299**:690-4.
- Anonymous. Which drug for hypertension? *Br Med J* 1978;ii:75-6.
- Morgan TO, Adams WR, Hodgson M, Gibberd RW. Failure of therapy to improve prognosis in elderly males with hypertension. *Med J Aust* 1980;**2**:27-31.
- Morris GK, Mitchell JRA. The clinical management of venous thromboembolism. *Br Med Bull* 1978;**34**:169-75.
- Medical Research Council Working Party on Mild to Moderate Hypertension. Report. Randomised controlled trial of treatment for mild hypertension: design and pilot trial. *Br Med J* 1977;ii:1437-40.
- Kirkendall WM, Hammond JJ. Hypertension in the elderly. *Arch Int Med* 1980;**140**:1155-61.

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