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Dexamethasone in acute stroke

GRAHAM MULLEY, R G WILCOX, J R A MITCHELL

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Summary and conclusions

Over 13 months 118 patients admitted to hospital with acute stroke were allocated at random to treatment with either dexamethasone or placebo. At one year there was no significant difference in the numbers of survivors or in the quality of life between the two groups.

The results suggest that there is no indication for the routine administration of dexamethasone to a heterogeneous group of patients with stroke.

Introduction

Cerebral oedema is considered to be a major cause of death in acute stroke.[1] If the brain swelling could be reduced quickly a faster and more complete recovery might be expected. Cerebral oedema associated with cerebral tumour often responds well to steroids, but studies of steroids in acute stroke have been generally disappointing. Such studies have included relatively few patients who were followed up over a short period; they have been described as "poorly documented, inconsistent and controversial."[2] Despite this, many physicians continue to treat stroke with dexamethasone.

As most patients with stroke present to general physicians in district general hospitals rather than to specialised neurological centres we have carried out a double-blind study to see whether intramuscular dexamethasone modifies survival or residual incapacity after stroke.

Patients and methods

During a 13-month period all patients admitted to four adjoining medical wards at this hospital with a presumptive diagnosis of stroke were considered for the study. At the initial assessment we excluded (*a*) patients who had had a previous stroke; (*b*) those in whom the stroke had occurred more than 48 hours before admission; (*c*) those whose neurological deficit was considered likely to be due to an intracranial tumour, injury, or subarachnoid haemorrhage; and (*d*) those already receiving steroids at the time of admission. Patients with a history of diabetes mellitus or peptic ulcer or other conditions potentially exacerbated by steroids were included at the discretion of the admitting consultant physician. Patients who made a complete recovery within 24 hours of the onset of stroke were withdrawn from the trial.

After clinical assessment by the admitting medical team, a lumbar puncture, electrocardiography, and the following blood estimations were performed: blood count; erythrocyte sedimentation rate (ESR); urea, electrolyte, sugar, and cortisol concentrations; and the Wassermann reaction and Venereal Disease Research Laboratory test. The patient was then allocated to a course of treatment ampoules identified only by a code number. Each of the four wards held a series of sealed envelopes prepared in batches of 10 and containing randomised treatment instructions. The ampoules contained either 2 ml sterile water or 4·2 mg dexamethasone base in 2 ml sterile water. After entering a patient into the trial the next envelope was opened and the appropriate ampoules given intramuscularly every six hours for the first 10 days, eight-hourly on day 11, 12-hourly on days 12 and 13, and once on day 14. The blood count and electrolyte estimations were repeated on day 10, and the cortisol estimations on days 15 and 17—that is, one and three days after stopping the injections. The patients continued under the overall care of the admitting medical firm, who determined the need for further investigations or for antibiotics, parenteral nutrition, and physiotherapy.

The trial organisers (GM and RGW) visited the patients every day during their hospital stay. They recorded the admission details in each case and, for the first three months of the study, inspected the injection sites daily and asked about local discomfort in those patients who were conscious. They also assessed the severity of the stroke using the simple scoring system outlined in table I and added together the score for each variable. Thus 25 was the best score possible and 6 the worst. This assessment was repeated on day 10, at three months, and at 12 months, when a more detailed analysis of the quality of life was made by one of us (GM). When a patient died in hospital permission for necropsy was requested. The treatment code was available to JRAM, who did not participate in assessing the patients' progress and who regularly compared the death and disability rates in the two groups to ensure that it was ethical to continue with the study. This paper reports the outcome in the treatment and control groups up to 12 months' follow-up. Student's unpaired *t* test and the χ^2 test were used for comparisons.

TABLE I—*Scoring system used for stroke assessment*

Variable	Score
Conscious level:	
Deeply unconscious	2
Responds to pain	3
Drowsy	4
Alert	5
Speech:	
Aphasic	1
Severe dysphasia	2
Mild dysphasia	3
Normal	4
Urinary continence:	
Incontinent	1
Continent	3
Mobility:	
Bedfast	1
In a chair	2
Walks with two helpers	3
Walks with one helper	4
Walks with frame	5
Walks unaided for short distance	6
Walks normally	7
Arm function:	
No movement	1
Some movement, no function	2
Able to feed using affected arm	3
Able to dress	4
Able to wash	5
Normal	6

Results

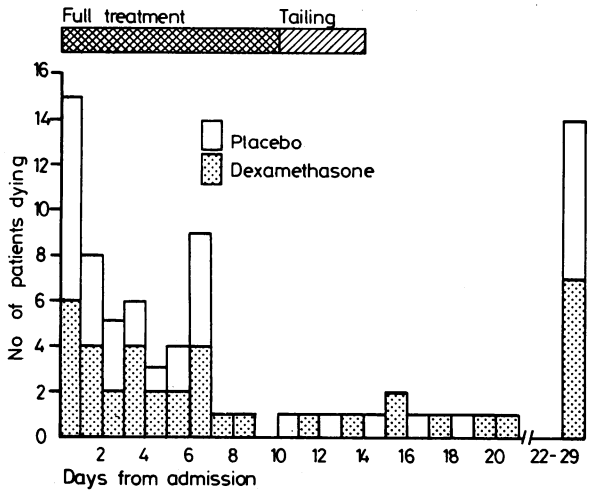
From 1 March 1976 to 31 March 1977, 256 patients with a presumptive diagnosis of stroke were admitted to the four participating wards. Of these, 113 were ineligible for the study for the following reasons: previous stroke (51), stroke occurring more than 48 hours before admission (27), diagnosis of stroke not confirmed after examination (15), subarachnoid haemorrhage considered more likely (10), death before full assessment (7), and already receiving steroids (3). In addition seven patients were excluded in error and two at the request of the admitting consultant. Of the 134 patients randomised to receive dexamethasone or placebo, 16 were subsequently withdrawn and are considered separately. The following results therefore refer to the 118 patients who remained in the study, 61 of whom received dexamethasone and 57 placebo injections.

Department of Medicine, General Hospital, Nottingham NG1 6HA
GRAHAM MULLEY, MB, MRCP, clinical research fellow
R G WILCOX, BSC, MRCP, lecturer in medicine
J R A MITCHELL, MD, FRCP, professor of medicine

The two groups were well matched on admission for age, sex, total neurological scores, previously known hypertension or diabetes mellitus, and the presence of atrial fibrillation.*

OUTCOME

The figure shows the mortality rates in the two groups during the first three months and indicates that the short tailing-off period adopted for dexamethasone was not accompanied by any increase in deaths. The inability of dexamethasone to influence outcome either acutely or in the long term is shown in table II. The high overall death rate by three months (63%) was due to the relatively short time lapse between the onset of stroke and admission to hospital (five and a half hours), for in the 27 patients who were excluded from the study because their stroke had occurred more than 48 hours before admission the three-month death rate was 34%.



Mortality in the two treatment groups during first three months after admission.

TABLE II—*Death rates in the two treatment groups to end of follow-up*

	No (%) dead at 10 days	No (%) dead at 3 months	No (%) dead at 12 months
Dexamethasone group (n = 61)	25 (41)	38 (62)	42 (69)
Placebo group (n = 57)	27 (47)	37 (65)	45 (79)

TABLE III—*Grades of disability recorded in the two groups of survivors at 12 months. (Adams's method[3])*

	Dexamethasone group	Placebo group
Grade 1 (fully independent; normal intellect; some use of affected arm; confident walk)	10	8
Grade 2 (walks unaided but arm useless; needs help dressing and with toilet; continent; may have intellectual impairment)	5	1
Grade 3 (chairbound or bedbound; often confused; usually incontinent)	4	3
Total	19	12

Of the 118 patients admitted to the study, 87 (74%) were dead at 12 months—namely, 42 given dexamethasone, and 45 given placebo. Thus there was no significant difference in survival between the two groups. There was also no significant difference between the two groups of survivors in age, sex, total neurological score on entry, or history of hypertension or diabetes mellitus.

Morbidity—The durations of stay in hospital were the same in the two groups. At 12 months the two groups of survivors were comparable in respect of physical disability graded by the method of Adams[3] (table III). Of the 19 survivors in the dexamethasone group, 16 were at home at 12 months compared with eight of the 12 placebo survivors. This small difference was probably due to the uneven distribution of unmeasured social factors in the two groups.

*Full details are available from RGW.

CORTISOL AND POTASSIUM CONCENTRATIONS AND DIABETES

Plasma cortisol concentrations were measured on admission, on day 15 (the day after the last injection), and on day 17 to assess any continued adrenal suppression. The initial concentrations in the two groups were comparable. Table IV gives the mean concentrations in those survivors for whom full data were available. The results show that dexamethasone given in the schedule adopted for this trial may be safely tailed-off over a very short period.

The lack of mineralocorticoid effect of dexamethasone was shown by the serum potassium concentrations, which were 3·7 ± SE of mean 0·1 mmol(mEq)/l on the day of admission and 4·2 ± 0·1 mmol/l on day 10. No patient given dexamethasone developed glycosuria, and none of the diabetics given the drug presented difficulties with control.

TABLE IV—*Mean (± SE of mean) plasma cortisol concentrations in survivors in the two treatment groups (numbers of patients in parentheses). Values are nmol/l.*

	Dexamethasone group	Placebo group
On admission	864 ± 119 (22)	761 ± 92 (16)
On day 15	444 ± 51** (22)	582 ± 46* (15)
On day 17	697 ± 48 (17)	621 ± 52 (16)

Compared with values on admission: *P < 0·05; **P < 0·01.
Conversion: SI to traditional units—Plasma cortisol: 1 nmol/l ≈ 0·04 μg/100 ml.

CEREBROSPINAL FLUID

While recognising the limitations of cerebrospinal fluid (CSF) examination, we attempted to classify the stroke crudely as a haemorrhage or an infarct on the basis of the red cell count in the CSF. From the patients who came to necropsy (n = 33), of whom 23 had had a lumbar puncture on admission, we found that the presence of fewer than 400×10^6 red cells/l CSF (400/mm³) was unlikely to be associated with cerebral haemorrhage, and that more than 400×10^6/l was unlikely to be associated with a cerebral infarct. We found no particular benefit of dexamethasone in patients with CSF red cell counts of under and over this value.

COMPLICATIONS OF TREATMENT

For the first three months of the study we inspected the injection sites daily and questioned the patients and nursing staff about discomfort. No patient developed local complications from the injections, and only one complained of local discomfort. A 74-year-old man with left hemiplegia who received dexamethasone developed pulmonary tuberculosis. His ESR on admission was 10 mm in the first hour, and a chest *x*-ray film showed old apical disease. He deteriorated during the second week; his ESR rose to 110 mm, and radiography then showed diffuse pulmonary shadowing. He was alive and at home at 12 months.

WITHDRAWALS

Of the 134 patients initially randomised into the study, 16 were withdrawn when other information became available. In five other diagnoses were made—namely, subarachnoid haemorrhage (2), cerebral tumour (1), demyelinating disease (1), and ethanol overdose (1). Five patients were withdrawn because it emerged that they had had previous strokes or a duration exceeding 48 hours; four patients (two in the placebo group, two in the dexamethasone group) made such rapid progress that the admitting physician wished to send them home after only a few days. One patient was withdrawn because he developed tuberculosis; and one patient was withdrawn at the request of the admitting consultant physician.

Discussion

We failed to reduce mortality or improve the quality of life by giving dexamethasone to a heterogeneous group of patients with stroke. This agrees with the findings of Bauer and Tellez,[4] who reported no significant difference between steroid and placebo in 54 patients with acute stroke who were neurologically assessed at 14 days.

There were several important differences between our study and previous studies. Early trials of steroid treatment in acute stroke were not controlled.[5–7] Other studies have not randomly allocated patients to treatment and placebo groups.[8 9] In the four double-blind studies using dexamethasone[4 10–12] the numbers of patients were small (54, 53, 31, and 19 respectively) and the final clinical assessment was made in the first month after the stroke. We followed up 118 patients for a year and used mortality and quality of survival as indices of effectiveness of treatment. We included all clinically diagnosed first-time strokes whatever the patients' level of consciousness and regardless of whether or not blood was found in the CSF, whereas Bauer and Tellez[4] and Rubinstein[12] confined their studies to patients with impaired consciousness. In two studies[4 10] lumbar puncture was done in all cases, and those patients who were thought to have cerebral haemorrhage were excluded. None of the previous studies mentioned whether or not patients who were known to have had previous strokes were included. The dose of dexamethasone and duration of treatment also differed in each study. We gave a total of 192 mg in 14 days; Rubinstein[12] gave 52 mg in three days, Bauer and Tellez[4] 120 mg in 10 days, and Patten *et al*[11] 220 mg in 17 days.

The mortality rate in our study (63% at three months) was much higher than in other studies. There were no deaths at 17 days in the study of Patten *et al*,[11] while the remaining studies had mortality rates of 22% at 14 days,[4] 22% at 28 days,[10] and 42% at three days.[12] This may reflect different admission procedures. When our hospital is receiving emergencies it is responsible for admitting all acute medical cases from a catchment area of some 500 000 people. The time between onset of stroke and arrival at hospital is therefore short, averaging five and a half hours (table A*).

Randomisation proved difficult in the previous studies. Although our groups were well matched for age, sex, blood pressure on admission, side of stroke, and interval between stroke and admission, more patients in the dexamethasone group were fully conscious on admission, and there were twice as many patients in the placebo group who responded only to painful stimuli. Nevertheless, analysis of the outcome in patients who had impaired consciousness on admission showed no difference between the two groups. Of the 73 patients with impaired consciousness, 31 received dexamethasone and 42 placebo. At one year only 12 of these patients were alive. Four of the survivors had received dexamethasone, and three of these were at home; eight had received placebo, seven of whom were at home. None of the patients who were deeply unconscious on admission (seven given dexamethasone, eight placebo) was alive at one year.

We had considerable misgivings about the administration of placebo injections to patients, most of whom were too ill to give informed consent. As we were making subjective assessments of disability and quality of life we thought that it was essential to ensure that the study was double-blind. No patient developed complications at the injection sites, and when questioned directly at three months only one patient said that the injections had been painful.

Possibly the concept of cerebral oedema after stroke is mistaken. In cerebral oedema associated with brain tumour there is considerable brain swelling, the oedema around the tumour often causing more neurological deficit than the tumour itself.[2] This oedema is mainly a result of altered permeability of capillary endothelial cells (vasogenic oedema), and it responds well to dexamethasone. In cerebral thrombosis, extensive cerebral oedema is usually a consequence of occlusion of a major cerebral vessel. A pathological study[13] showed that only 13% of patients dying of cerebral infarction have severe oedema. Moreover, much of this oedema is due to swelling of nerve cells (cytotoxic oedema), and this type of brain swelling does not respond to steroids.[14] The use of computerised axial tomography to determine the existence, nature, and extent of brain oedema will be helpful in any future studies but is not available to clinicians in district general hospitals, to whom most patients with stroke present.

Our study shows that until these areas of doubt are resolved there is no indication for the routine administration of dexamethasone to a heterogeneous group of patients with stroke.

*Table A may be obtained from RGW.

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Full details of the patients and copies of table A may be obtained from Dr R G Wilcox.

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ONE HUNDRED YEARS AGO The correction of idleness and misconduct during confinement by reduction of food is a very serious matter. The habitual diet ought to be as low as is consistent with health; and we must understand that, in reducing it, we are administering corporal punishment. The victim will lose flesh and power of resistance as infallibly as he loses leather in a flogging, and he will certainly be put to pain. But let society beware of discarding in too great a hurry survivals of more barbarous states of civilisation, till it is proved that they are not needful safeguards. The reporters are of opinion that, to secure the purposes of punishment for prison-offences, the plan of reducing the diet to a scale as low as one pound of bread *per diem* should be continued. The worst of all corporal punishment is, that it cannot be fairly graduated to the offence; for, while three days' bread and water is not too much to act as a deterrent to very moderate offenders, to continue its infliction over that time results in injury beyond what is designed. It may be suggested, however, that the three days' fast can easily be repeated over and over again after an interval, just as floggings are administered in moderate doses weekly or fortnightly to brutal offenders. Thus the strong moral influence of anticipation is brought into play, whilst danger to health is not incurred. The power of the stomach as an implement of education, moral and intellectual, is the subject of a familiar quotation from an observant poet, and it is a pity to surrender any power left us of improving the manners of criminals. (*British Medical Journal*, 1878.)