PAPERS AND ORIGINALS

Combined dexamethasone and low-molecular-weight dextran in acute brain infarction: double-blind study

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Summary

Intramuscular dexamethasone combined with intravenous low-molecular-weight dextran (dextran 40) was compared with placebo in 40 patients with acute ischaemic cerebral infarction. A double-blind procedure was used. Dexamethasone was given for up to 14 days and dextran 40 for up to three days after the infarction. A weighted scoring system was used to evaluate neurological state and mobility. There were no differences in mortality or in improvement of the neurological or mobility scores between the two groups.

Introduction

The multiplicity of treatments that have been tried in acute cerebral infarction reflects the ineffectiveness of current management.¹ Corticosteroids reduce cerebral oedema associated with brain tumours,² and prevention and control of cerebral oedema in acute brain infarction might be expected to lessen further tissue damage. Infusion of low-molecular-weight dextran increases circulation in ischaemic brain infarction,³ and this might help ischaemic neurones to survive.

We have evaluated the effects of combined dexamethasone and low-molecular-weight dextran in acute brain infarction.

Patients and methods

Forty patients aged under 66 were studied over four weeks. All had a history of more than 24 hours of a focal neurological deficit of sudden

onset caused by cerebral infarction. The limit of 24 hours was used to exclude transient ischaemic attacks. Treatment was started 24-48 hours after the onset of symptoms with either dexamethasone plus low-molecular-weight dextran (dextran 40) or placebo, the patients being allocated at random to either group.

We excluded the following conditions: acute myocardial infarction, severe hypertension, overt heart or renal failure, recent gastric or duodenal ulcer, severe psychiatric disturbance, and systemic infection. None of the cerebrospinal fluid samples contained more than 200 red blood cells $\times 10^3/l$. All patients were subjected to detailed general and neurological assessment, cerebrospinal fluid examination, serial brain scanning, skull and chest radiography, and routine haematological and urine analyses. Cerebral angiography was performed in 30 cases. All patients who died came to necropsy.

Neurological assessment was done on admission and again on the 8th, 15th, 22nd, and 29th days. Assessment comprised level of consciousness, mental state, degrees of motor deficit (each limb scored separately) and aphasia, cranial nerve function, and reflexes. Each deficit was given a raw score of 0-3 (0 normal; 1 mild; 2 moderate; 3 severe), and mobility scored 0-6 (0 walks unaided; 1 walks aided; 2 stands unaided; 3 stands aided; 4 sits unaided; 5 sits aided; 6 bedridden). Since the functional effects of the disabilities were not fully comparable each raw score was multiplied by a weighting factor to give a final, corrected score.⁴ Weighting factors ranged from 1 to 20 as follows: level of consciousness $\times 20$, mental state $\times 10$, degree of motor deficit $\times 10$ (each limb scored separately), degree of aphasia $\times 7$, cranial nerve function $\times 3$, reflexes $\times 1$, and mobility $\times 20$.

Dexamethasone, dextran 40, and placebo were in identical phials bearing the patient's number. We were unaware of the identity of the phials being used, the code being broken only after final evaluation of the patients' conditions. The active treatment was given as follows: dexamethasone, 10 mg intramuscularly initially, followed by 5 mg six-hourly for seven days, then tapering to zero over seven days (total dose 215 mg); dextran 40, a loading dose of 500 ml intravenously over one to two hours, followed by 500 ml/12 hours for 72 hours. Placebo was given in amounts identical with those of the active drugs—0.9% NaCl in place of dexamethasone, and 10% glucose in place of dextran 40. No vasodilators were used. Three patients received anticoagulants in the third week because of deep vein thrombosis in the leg. General medical care was the same in all cases.

Student's *t* test and the χ^2 test were used in statistical comparisons.

Results

The active treatment and control groups were comparable in age, sex, side of cerebral infarction, and site of occlusion of major cerebral arteries as verified angiographically or at necropsy (table I). There

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TABLE I—Characteristics of active treatment and control groups

Group	No of patients	Mean age in years	Sex		Side of cerebral infarction		Site of occlusion of major cerebral artery			
			M	F	L	R	Internal carotid	Middle cerebral	Subdivision of middle cerebral	Not known
Active treatment	20	48.5	15	5	6	14	5	6	5	4
Control	20	45.9	16	4	9	11	4	4	6	6

were no significant differences in the pretreatment neurological, mobility, or total scores between the two groups (tables II-IV).

In the acute phase after the stroke 11 patients in each group were bedridden, and four weeks after the stroke 15 patients in each group could walk. Fourteen patients in the active treatment group and 13 of the controls improved, and four and six patients in the two groups respectively were unchanged (table V). In the active treatment group, four of the 14 patients who improved and one of four who were unchanged suffered a reversible worsening of their initial neurological scores in the first days of treatment. Among the controls only one of the 13 patients who improved and none of those who were unchanged had such reversible worsening. This difference between the two groups is significant ($P < 0.05$).

Two patients in the active treatment group and one of the controls died in the first week. Necropsy showed massive cerebral oedema in all three. One further patient in the active treatment group died from infarction of the contralateral hemisphere on the 21st day after the initial stroke.

There were no significant differences in the initial or subsequent neurological, mobility, or total scores between the two groups (tables II-IV) or in the incremental changes of these scores.

After three days' treatment one patient in the active treatment group had a reversible psychotic episode lasting a couple of days. Deep vein thrombosis of a leg verified by phlebography occurred in three

patients in the active treatment group in the third week after the stroke. All were given anticoagulants; none experienced pulmonary embolism.

Discussion

This appears to be the first study of the combined effects of dexamethasone and low-molecular-weight dextran in the acute stage of brain infarction. The results must therefore be compared with those obtained with either dexamethasone or low-molecular-weight dextran alone.

In a double-blind study, Patten *et al*⁵ found dexamethasone to be beneficial in acute stroke. But when cerebral haemorrhages are excluded the results are less convincing. Furthermore, they did not evaluate the level of consciousness, which is usually regarded as a sensitive index of cerebral oedema. The results of more recent studies^{4, 6} do not support the use of dexamethasone in acute stroke.

In a double-blind study of 100 patients with acute stroke favourable effects were reported with low-molecular-weight dextran.⁷ This claim, however, was based solely on near-significant improvements in mentation, reflexes, and total neurological state, the degree of functional recovery of the patients being ignored. Later studies failed to show any beneficial effect of low-molecular-weight dextran.^{8, 9}

None of these studies presented unequivocal evidence that patients who might have been bedridden would have been able to achieve a wheelchair life, or that those who might only have been able to walk aided would have become independent. We have now failed to show any beneficial effects of the simultaneous use of dexamethasone and low-molecular-weight dextran in acute brain infarction. Two patients in our active treatment group and one of the controls died from severe brain oedema. The active treatment also failed to stop the progression of brain oedema after the stroke, as shown by the reversible worsening of the neurological deficit in five patients. The treatment did not change the natural history of the acute brain infarction, as shown by the similar improvement in neurological state and mobility in the active treatment and control groups. In the acute stage 11 patients in each group were bedridden, and at the end of four weeks 15 patients in each group could walk.

Our results do not support the combined use of dexamethasone and low-molecular-weight dextran in acute brain infarction.

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TABLE II—Means of weighted neurological scores in active treatment and control groups. Results expressed $\pm$ SD

Group	Days after stroke				
	1	8	15	22	29
Active treatment	56.2 $\pm$ 22.4	49.4 $\pm$ 28.0	48.4 $\pm$ 27.1	43.3 $\pm$ 24.1	41.6 $\pm$ 24.1
Control	51.2 $\pm$ 21.9	45.1 $\pm$ 22.3	42.6 $\pm$ 26.6	40.3 $\pm$ 26.5	39.6 $\pm$ 26.1

TABLE III—Means of transfer capacity scores in active treatment and control groups. Results expressed $\pm$ SD

Group	Days after stroke				
	1	8	15	22	29
Active treatment	81.0 $\pm$ 47.5	60.6 $\pm$ 45.6	37.6 $\pm$ 42.4	22.5 $\pm$ 30.0	21.3 $\pm$ 27.8
Control	67.0 $\pm$ 55.2	47.4 $\pm$ 45.8	40.0 $\pm$ 45.2	28.4 $\pm$ 40.7	25.3 $\pm$ 42.1

TABLE IV—Means of total scores in active treatment and control groups. Results expressed $\pm$ SD

Group	Days after stroke				
	1	8	15	22	29
Active treatment	137.2 $\pm$ 76.2	105.8 $\pm$ 71.9	86.5 $\pm$ 66.1	65.8 $\pm$ 48.8	62.8 $\pm$ 47.9
Control	118.2 $\pm$ 75.3	91.9 $\pm$ 66.7	82.6 $\pm$ 69.5	67.6 $\pm$ 63.4	64.8 $\pm$ 69.1

TABLE V—Results of treatment

	Active treatment group	Control group
No improved	14	13
No unchanged	4	6
No died	2*	1
No with reversible worsening	5	1

*A further patient died from new infarction of contralateral hemisphere on 21st day after initial stroke.