Original article

Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy

N. S. Lennard, C. Vijayasekar, C. Tiivas, C. W. M. Chan, D. J. Higman and C. H. E. Imray

Coventry and Warwickshire County Vascular Unit, Coventry and Warwickshire University Hospitals, Walsgrave Hospital, Clifford Bridge Road, Walsgrave, Coventry CV2 2DX, UK
Correspondence to: Mr C. H. E. Imray (e-mail: chrisimray@aol.com)

Background: **Transcranial Doppler (TCD)-directed Dextran 40 treatment after carotid endarterectomy reduces the rate of early postoperative thrombosis. This study assessed the efficacy of intravenous Dextran 40 at controlling symptoms and emboli before elective carotid endarterectomy in patients with recurrent or crescendo transient ischaemic attacks (TIAs).**
Methods: **In a prospective study, patients with more than 70 per cent internal carotid artery stenosis who had two or more symptomatic episodes within 30 days and TCD-detected microemboli were studied. Dextran 40 was commenced at 20 ml/h and TCD was repeated to reassess the rate of embolization. The infusion was increased in 20-ml/h increments until symptoms and emboli were controlled. The patient then had carotid surgery on the next elective list.**
Results: **Nineteen patients with internal carotid stenosis greater than 70 per cent, recurrent symptoms and TCD-detected emboli were studied. All patients had symptoms and emboli controlled with Dextran 40. One patient with both unstable angina (awaiting urgent operation) and crescendo TIAs died from a myocardial infarct before undergoing operation. Of the 18 patients who had an operation, one suffered a non-disabling stroke on the third postoperative day.**
Conclusion: **TCD-directed Dextran 40 offers a safe approach to high-risk patients before elective carotid endarterectomy, and warrants further study.**

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Introduction

Stroke is a major cause of morbidity and mortality; it is the third commonest cause of death in the Western world. There were an estimated 133 800 strokes in England and Wales in 1999[1] and carotid artery disease is thought to be responsible for up to 25 per cent of strokes[2]. Of these, approximately 15 per cent will have a warning transient ischaemic attack (TIA). Carotid endarterectomy, combined with maximal medical therapy in selected symptomatic patients, has been shown to be superior to maximal medical therapy in two large prospective randomized trials[3,4].

The risk of stroke is highest after the first TIA; 4–8 per cent of strokes occur in the first month and 12 per cent in the first year[5,6]. The optimal treatment of patients with recurrent or crescendo TIAs is uncertain. Based on the poor outcome of patients with crescendo TIAs with medical treatment alone, an aggressive approach with urgent carotid endarterectomy has been advocated[7]. However, the published results of emergency carotid surgery are variable, with complication rates ranging from no deficit in 12 patients, to an operative mortality rate as high as 20 per cent and neurological deficit in up to 40 per cent of patients in other series[8–14].

The aim of this study was to assess whether preoperative transcranial Doppler-directed intravenous Dextran therapy might control symptoms and emboli prior to elective carotid endarterectomy.

Patients and methods

Between November 1998 and July 2001, 19 patients were recruited into this prospective pilot study. Patients were seen in an open-access carotid duplex clinic, having been referred either by their general practitioner or by a hospital consultant. The vascular unit serves a population of 950 000.

Duplex imaging of both carotid arteries was performed by one of three vascular technologists. An internal carotid artery peak systolic velocity of 200 cm/s was used to define patients with more than 70 per cent stenosis, in accordance with the criteria of the European Carotid Surgery Trialists' Collaborative Group.

Patients who had two or more episodes of transient cerebral or retinal ischaemia within the previous month underwent transcranial Doppler (TCD) ultrasonography of the symptomatic middle cerebral artery using a PC Dop 842 (SciMed, Fishponds, Bristol, UK) with a 2-MHz probe focused on the middle cerebral artery at 4·5–5·5 cm using a sample volume length of 1·1 cm for 1 h. One of three experienced vascular technicians observed the TCD signals for embolic signals by listening for their characteristic sound and spectral appearance, using published identification criteria[15]. All patients had been on antiplatelet therapy at the time they experienced the symptoms.

Patients with internal carotid artery stenosis greater than 70 per cent, ipsilateral middle cerebral artery embolization, and a history of two or more TIAs within the previous month in the appropriate carotid territory were included in the trial.

Patients were admitted to the vascular ward and commenced on an intravenous infusion of Gentran 40® (Dextran 40 intravenous infusion BP, 10 per cent w/v, in glucose intravenous infusion BP, 5 per cent w/v; Baxter Healthcare, Thetford, UK). An initial 20-ml bolus was given, and the infusion was then run at 20 ml/h. Once the Dextran 40 had been running for at least 2 h, TCD scanning was repeated to reassess the rate of embolization. If the patient continued to have emboli, or had further symptoms of cerebral or retinal ischaemia, the rate of the Dextran 40 infusion was increased at increments of 20 ml/h until the symptoms and emboli were controlled. All patients were treated with either aspirin 75–150 mg or clopidogrel 75 mg daily, and with enoxaparin 20 mg daily.

These patients proceeded to carotid endarterectomy on the next available elective list, allowing time for routine surgical work-up. The Dextran 40 infusion was stopped 2 h before operation.

Results

Nineteen patients (13 men) were included in the study; their ages ranged between 38 and 86 years. Fourteen patients had recurrent hemisensory or hemimotor symptoms, and five had recurrent amaurosis fugax. Eight patients had coexisting ischaemic heart disease and two were awaiting coronary artery bypass surgery. One patient was an insulin-dependent diabetic. The number of symptomatic episodes suffered by each patient ranged from two episodes within 10 days to four episodes within 24 h. The number of emboli detected by TCD ultrasonography before institution of the Dextran 40 infusion ranged from two to nine per h. No patient had any recurrent neurological symptoms, and all had their emboli controlled while on the Dextran 40 infusion. Sixteen patients required Dextran 40 at a rate of 20 ml/h, two needed a rate of 40 ml/h and one needed 100 ml/h to abolish the emboli.

Carotid endarterectomy

The time from commencement of the Dextran infusion to carotid endarterectomy ranged from 1 to 10 days. The majority had the operation within 5 days, although one patient with recurrent right hand weakness and coexisting headache required investigation with computed tomography and magnetic resonance agniography, which prolonged the wait before operation. The Dextran was infused continuously until the day of operation in all patients.

All but one of the carotid endarterectomy procedures were performed under locoregional anaesthesia. In these patients, shunting was determined by awake-testing and near-infrared cerebral spectroscopy. In the patient who had general anaesthesia, the need for shunting was determined using standard TCD criteria. All patients were monitored in the immediate postoperative period with TCD ultrasonography, and four patients required a Dextran 40 infusion after operation to control continued embolization.

One patient died before operation. This 79-year-old woman was on the coronary care unit, requiring intravenous nitrates for angina and awaiting urgent coronary artery bypass grafting. She also experienced recurrent episodes of cerebral ischaemia. She was commenced on a Dextran 40 infusion at 20 ml/h, which controlled her symptoms and emboli; however, she developed congestive cardiac failure and suffered a fatal myocardial infarction.

Of 18 patients who underwent carotid endarterectomy, one suffered a non-disabling stroke on the third postoperative day (early carotid occlusion based on duplex imaging). The stroke resolved fully at 6 weeks. Seventeen patients recovered without either neurological or cardiac complications. Four patients developed a minor wound haematoma after operation, but none required surgical intervention. One patient developed moderate renal impairment following preoperative Dextran therapy; however, this resolved fully on conservative management before discharge.

Discussion

TCD monitoring allows continuous non-invasive assessments of middle cerebral artery velocity, which is closely related to cerebral blood flow. It is also possible to measure transient microemboli signals or high-intensity transient signals. Microemboli are a common phenomenon in patients with acute stroke and may continue for some days after the acute event[16]. The presence of microemboli is a significant independent predictor of early recurrence in patients with stroke or TIA of arterial origin[17].

In asymptomatic patients with a critical internal carotid artery stenosis[18] when the microemboli rate was greater than two per hour in the ipsilateral middle cerebral artery, there was an increased risk of developing ischaemia (odds ratio 31 (95 per cent confidence interval (c.i.) 3 to 302); $P = 0{\cdot}005$). In a study[20] of both symptomatic and asymptomatic patients with carotid stenosis greater than 60 per cent, the presence of embolic signals gave an adjusted odds ratio for future TIA or stroke of 8·1 (95 per cent c.i. 1·6 to 41·6); $P = 0{\cdot}01$). The presence of high-intensity transient signals may therefore define a subgroup of patients with a critical stenosis who may be at greater risk of stroke[19].

TCD sensitivity to the presence of particulate emboli can help to guide surgical dissection during carotid endarterectomy, allowing changes in surgical technique or strategy (such as early carotid clamping)[21]. A microemboli signal count greater than 50–100 per h in the early postoperative phase after carotid endarterectomy is also predictive of the development of ipsilateral focal ischaemia[22,23].

Postoperative TCD-detected high-intensity transient signals are almost always platelet aggregates generated by a partially denuded, highly thrombogenic, vascular endothelium. Unchecked, these aggregates may mature into occlusive thromboemboli, resulting in infarcts in succeeding hours or days. Lennard *et al.*[24] found that signs of persistent embolization, characterized by more than 25 high-intensity transient signals in 10 min, consistently preceded injury[24]. Embolization was completely prevented by incremental infusion of Dextran 40. The same workers have now audited 600 consecutive procedures, following the introduction of TCD-directed Dextran therapy, and the rate of thrombotic stroke after carotid endarterectomy fell from 2·7 per cent to zero (eight strokes prevented)[25,26]. Six hours of postoperative TCD monitoring is impractical outside a research programme; however, the technique appears to work in 3 h, and there is evidence that 30 min of monitoring may be adequate[27].

The rheological improvement caused by Dextran 40, together with its effect of decreased platelet adhesiveness and reduced factor VIII activity, is well recognized[28]. It has been further postulated that there is a coating effect on the denuded artery, which decreases electronegativity and increases clot lysability, both of which might make this agent a useful adjunct in preventing graft or endarterectomy-associated thrombosis. It should be noted that Dextran may interfere with cross-matching blood, cause bleeding, renal failure or occasionally acute allergic reaction. In addition, it can precipitate cardiac failure, as happened in the only patient to die in this series.

The study suggested a possible role for TCD in the preoperative management of symptomatic carotid stenosis. It also showed that it is possible to treat recurrent or crescendo TIAs with a combination of aggressive medical therapy and elective surgery. In this study, when emboli were controlled, neurological symptoms stopped. While a single embolus does not cause a TIA, a high embolic load indicates that an individual is at greater risk of further neurological events. As Dextran 40 has no known effect on cholesterol emboli, it could be speculated that the recurrent symptoms controlled by the antiplatelet agent must have been caused by platelet emboli.

The efficacy of medical treatment could be assessed with TCD. Although most of the emboli were controlled with a low dose of Dextran 40, a small number of patients (three of 18) required considerably higher doses. Failure to control either emboli or symptoms with TCD-directed Dextran and adjuvant medical therapy could be an indication for urgent carotid endarterectomy. Patients with symptoms but without emboli, and patients with emboli and no symptoms, were excluded from this study.

If the results of this study are confirmed, there may be important implications regarding the management of recurrent TIAs. All patients would require duplex scanning to determine the state of the ipsilateral internal carotid artery. The presence of a critical internal

carotid artery stenosis would necessitate a TCD study to interrogate the middle cerebral artery for high-intensity transient signals. Medical therapy could then be instigated, and the efficacy of various pharmacological interventions assessed by confirming the control of symptoms and high-intensity transient signals. Elective surgery could then be considered if appropriate. Further study is warranted, in particular to examine how this control might influence the timing of carotid surgery.

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