Q J Med 2004; **97**:273–279
doi:10.1093/qjmed/hch054

Original papers

QJM

Improving the efficiency of delivery of thrombolysis for acute stroke: a systematic review

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Received 20 November 2003 and in revised form 13 January 2004

Summary

Background: Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) is licensed for use within 3 h of acute ischaemic stroke. The less the delay to treatment, the more likely it is to be effective.
Aims: To assess the effectiveness of interventions designed to overcome barriers to rapid administration of thrombolytic therapy.
Design: Systematic review of previous clinical studies.
Methods: We searched for studies that evaluated the effect of an intervention to reduce delays to administration of rt-PA. We searched MEDLINE, EMBASE, the trials register of the Cochrane Stroke Group, and the Cochrane Controlled Trials Register. We sought randomized and non-randomized controlled trials, before-and-after studies, interrupted time series, and observational studies.
Results: We identified 10 non-randomized studies that evaluated interventions that could speed up admission to hospital and administration of rt-PA. The types of interventions included: (a) education programmes for the public to improve their knowledge about symptoms of acute stroke; (b) training programmes for paramedical staff to improve their accuracy of stroke diagnosis and hasten transport of the patient to hospital; (c) helicopter transfer of patients to hospital; (d) training programmes in acute stroke therapy for emergency department staff; and (e) re-organization of in-hospital systems to streamline acute stroke care. Several programmes were multifaceted interventions.
Discussion: We identified important areas that could be targets for interventions to improve the efficiency of delivering thrombolysis for acute stroke. Multifaceted programmes might be more likely to be successful in reducing delays to therapy.

Introduction

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) has recently received a European license for treatment of acute ischaemic stroke. The benefit of thrombolysis is the greatest when given very early after stroke; rt-PA administered within 3 h of ischaemic stroke onset can

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reduce the absolute risk of being dead or dependent at 3 months by up to 16%.[1] Only a small proportion of patients are currently treated, although many more might be treated if they were brought to hospital and assessed more rapidly.[2–8]

Several types of barriers to early delivery of thrombolytic therapy have been described. Examples include: (a) delay in recognising the symptoms of stroke or seeking help;[9–11] (b) the general practitioner is contacted first, rather than the emergency services;[6,11,12] (c) stroke is triaged as non-urgent in the emergency department;[13–15] (d) delays in neuroimaging;[16,17] and (e) inefficient in-hospital acute stroke care.[9,11,12] The presence of these barriers means that many stroke patients are denied thrombolytic therapy,[18] and different interventions have been implemented to overcome them. This systematic review aimed to assess the effects of such interventions.

Methods

We sought to identify: (a) randomized controlled trials that compared an intervention with control, or one intervention versus another; (b) quasi-randomized trials; (c) non-randomized clinical studies; (d) before-and-after studies; (e) interrupted time series; and (f) uncontrolled observational studies. Studies were considered if they had assessed the delay to hospital admission and/or thrombolytic therapy, or the proportion of patients receiving thrombolytic therapy (usually within three hours).

We searched the trials register of the Cochrane Stroke Group, the Cochrane Controlled Trials Register (Central/CCTR) of the Cochrane Library (year 2002, issue 4), and MEDLINE and EMBASE, in December 2002. Titles, keywords and abstracts of all downloaded citations were screened, and paper copies of those meeting our selection criteria were retrieved. Two reviewers (JK, PAGS) independently assessed the methodological quality of all included studies and recorded their findings. Two reviewers (JK, PH) then extracted the data onto a pre-defined data extraction form. Full details of the search strategies are available from the authors.

Results

We scanned a total of 22 052 titles and abstracts, and retrieved 119 publications in full text. From these, we identified 10 studies that either described or evaluated the effects of interventions designed to improve the efficiency of delivering thrombolytic therapy for acute stroke.

Quality of the studies

We did not identify any randomized controlled trials. There were 10 non-randomized studies with a total of at least 6345 patients[19–28] (one study published in abstract form did not state the number of recruited patients[22]). Of these, four were before-and-after studies,[19,22,24,28] one was a non-randomized clinical study,[20] and five were observational studies.[21,23,25–27] Eight were carried out in the US, two in Canada and one in Germany. Only two studies stated that the patients were consecutively recruited.[20,27] The description of study methodology and the intervention was generally satisfactory.

Identified interventions

From these 10 studies, we identified different types of interventions that were hoped to improve the efficiency of delivery of thrombolytic therapy for acute stroke (Table 1). These interventions targeted both the pre-hospital and in-hospital phases of acute stroke care (Tables 2 and 3).

Combined educational programmes for the public, paramedical staff, and emergency department (ED) staff

Four studies evaluated these three types of interventions. The aim of educating the public was to improve the knowledge of symptoms of stroke, and emphasize the need to seek urgent help.

Table 1 Types of intervention designed to improve efficiency of delivering thrombolysis for acute stroke

Educational programmes for the public to improve knowledge of stroke presentation and need to call an ambulance if a stroke is suspected
Training programmes for the paramedical staff to improve accuracy of diagnosis, pre-hospital stroke care, and speed up transfer of patient to hospital
Helicopter transfer of stroke patients to hospital
Training programmes for the ED staff to improve and speed up acute stroke treatment including work-up for thrombolysis
Re-organization of in-hospital systems to streamline acute stroke care

Table 2 Types of intervention evaluated in the studies included in the systematic review

Study	Pre-hospital interventions			In-hospital interventions	
	Education for the public	Training programme for paramedics	Helicopter transfer of stroke patients	Training programme for ED staff	Re-organization of in-hospital system
Alberts 1992[19]	+		+	+	
Barsan 1994[21]	+	+		+	
Behrens 2002[24]		+		+	
Englander 1998[22]					+
Gomez 1994[20]					+
Harbison 1999[23]		+			
Hill 2000[25]	+	+		+	+
Morgenstern 2002[28]	+			+	
Riopelle 2001[26]		+		+	+
Silliman 2003[27]		+	+		

The aim of training the paramedical and ED staff was to speed up pre- and in-hospital stroke care, including the use of thrombolysis in selected patients.[19,21,24,28]

In study 1, Alberts *et al.* developed an educational programme for the public primary-care physicians and ED staff. This was supplemented by the use of helicopters for rapid transfer of patients to the specialist centre. This before-and-after study showed that, after the educational programme, the proportion of patients with ischaemic stroke arriving within 24 h of onset increased from 37% to 86%.[19]

In study 2, Barsan *et al*. developed an educational programme for the public, paramedical staff and ED staff. Over the course of this observational study (2.5 years), the mean delay from stroke onset to hospital arrival was reduced from 3.2 to 1.5 h. Simultaneously, the use of emergency services amongst admitted stroke patients increased from 39% in the first quartile of the study to 60% in the fourth quartile. Overall, 3.5% of patients received rt-PA.[21]

In study 3, Morgenstern *et al*. developed an educational programme for the public and ED staff; the public was also encouraged to be 'assertive in asking the physician about rt-PA'. This was a before-and-after study with a parallel comparison group. In the intervention group, the proportion of patients receiving rt-PA significantly increased from 1.4% to 5.8%; no significant difference was found in the parallel group.[28]

In study 4, Behrens *et al*. developed a training programme for paramedical and ED staff. The staff were trained in: (a) clinical assessment of patients with suspected stroke and the need to transfer them immediately to hospital; (b) rapid triage of stroke patients in the ED, resulting in urgent computed tomography (CT) scanning and administration of rt-PA or other forms of therapy. In this before-and-after study, the training programme reduced the mean delay from symptom onset to hospital arrival (5.2 to 3.3 h) and from diagnosis to start of therapy (2.6 to 1.6 h). The proportion of patients arriving within 3 h significantly increased from 2% to 15%, and the proportion receiving rt-PA increased from 2% to 11%.[24]

Specific training programmes for the paramedical staff to improve accuracy of diagnosis and speed up transfer of patient to hospital

Two studies evaluated this type of intervention.[23,27] In study 1, Harbison *et al*. designed a training programme for the paramedical staff to improve the accuracy of stroke diagnosis and speed up transfer of patients to hospital (the Rapid Ambulance Protocol). In this observational study, trained paramedical staff correctly diagnosed stroke or TIA in 83% of the patients, and the median delay from symptom onset to hospital arrival was 1.2 h. Delay to hospital arrival was greater if the general practitioner was initially contacted.[23] In study 2, Silliman *et al*. designed a training programme for the paramedical staff about the use of rt-PA in patients with acute stroke. This was supplemented by the helicopter transfer of potentially eligible patients to the specialist centre. In this observational study, of the 111 patients with suspected stroke transferred by helicopter, 71% arrived at the hospital within 3 h, and 21% received rt-PA.[27] The average cost of each helicopter transfer was $4623; helicopter charges were $3300 for lift-off plus $45 for every mile travelled. Although cost-effectiveness analysis was not conducted in this study, the

Table 3 Summary of the characteristics and results of the individual studies

Study	Year	Country	Design	*n*	Study findings
Alberts[19]	1992	USA	Before-and-after study	479	Delay from onset to arrival was reduced in patients admitted with ischaemic (but not haemorrhagic) strokes.
Barsan[21]	1994	USA	Observational study	2099	During the study (lasting 2.5 years), use of emergency services increased and delay from onset to hospital arrival declined. 59% of patients arrived <3 h and 77% <6 h. Overall, 3.6% of patients received rt-PA. Delay from onset to arrival was less if patients arrived by ambulance, were treated at the community rather than university hospital, and if stroke occurred in the afternoon.
Behrens[24]	2002	Germany	Before-and-after study	196	Pre- and in-hospital delays were reduced: from symptom onset to hospital arrival, and from diagnosis to start of therapy. Proportion of patients arriving <3 h and the proportion receiving rt-PA increased.
Englander[22]	1998	USA	Before-and-after study	Not stated	In-hospital delays were reduced: from hospital arrival to first medical assessment, from arrival to CT scanning, and from arrival to neurologist assessment. After intervention, mean delay from arrival to rt-PA administration (or decision not to treat) was 46 min.
Gomez[20]	1994	USA	Non-randomized clinical study	98 (consecutive)	All pre-hospital and in-hospital delays were reduced: from onset to hospital arrival, from arrival to code stroke activation, from code stroke activation to first medical assessment, and from first medical assessment to drug treatment.
Harbison[23]	1999	UK	Observational study	311	Paramedics correctly diagnosed stroke in 83% of patients. Mean delay from stroke onset to seeking medical help was 36 min, from seeking help to ambulance arrival was 6 min, from ambulance arrival to arrival at ED was 24 min. Delays were shorter if patients were transferred by ambulance rather than admitted by general practitioner.
Hill[25]	2000	Canada	Observational study	1127	During the study (lasting 3 years), pre- and in-hospital delays were reduced: from stroke onset to hospital arrival, from symptom onset to CT scanning, and from stroke onset to start of rt-PA. Between 1997 and 1998, 2.6% of patients received rt-PA.
Morgenstern[28]	2002	USA	Before-and-after study with parallel group	1733	Proportion of patients receiving rt-PA increased from 1.4 to 5.8% in the intervention group, where the increase was only from 0.5 to 0.6% in the parallel group.
Riopelle[26]	2001	Canada	Observational study	191	Overall, 22% of patients received rt-PA. Using an estimated figure of 792 strokes occurring in the entire region, 5.3% would have received rt-PA.
Silliman[27]	2003	USA	Observational study	111 (consecutive)	Overall, 71% of patients transferred by helicopter arrived at hospital <3 h, and 21% received rt-PA.

authors remarked, 'the increased costs (of using helicopter transfers) are small relative to the significant potential savings in rehabilitation and nursing home costs associated with this treatment modality'.[27]

Helicopter transfer of patients to hospital

This method of transferring patients to hospital was evaluated in Alberts et al and Silliman *et al.*, the results of which are described above.[19,27]

Re-organization of in-hospital systems to streamline acute stroke care

Two studies evaluated this type of intervention.[20,22] In study 1, Gomez *et al*. implemented a 'Code Stroke' protocol, which used a centralized pager system to alert all the members of the acute stroke team when a patient with suspected stroke arrived in the ED. This comparative study found that, compared with standard management, the 'Code Stroke' protocol significantly reduced the delay from hospital arrival to first medical assessment from 101 to 46 min, but there was no significant difference in delays from symptom onset to hospital arrival, or from first medical assessment to start of therapy.[20] In study 2, Englander *et al*. implemented a continuous quality improvement scheme which involved new algorithms and evaluation forms for assessing patients presenting with acute stroke. In this before-and-after study, after the introduction of the scheme, all in-hospital delays were significantly reduced, including delay from hospital arrival to first medical assessment (45 to 10 min), from hospital arrival to CT scanning (117 to 46 min), and from hospital arrival to neurologist assessment (76 to 46 min).[22]

Multifaceted programmes

Two studies evaluated multifaceted programmes that involved several types of interventions applied simultaneously.[25,26] In study 1, Riopelle *et al*. evaluated the Regional Acute Stroke Protocol (RASP) which contained three main elements: (a) training of paramedical staff; (b) training of ED staff including transfer of patients to nearby tertiary centre for thrombolysis; and (c) development of the acute stroke activation system at the regional stroke centre, which involved alerting the acute stroke team, immediate CT scanning, and administration of rt-PA. This observational study found that, of the 191 patients managed with the RASP, 42 (22%) received rt-PA. Using an estimated figure of 792 strokes occurring in the entire region, 5.3% would have received rt-PA.[25,26] In study 2, Hill *et al*. evaluated a multifaceted programme that included: (a) education of the public; (b) training of the paramedical staff and ED staff; (c) development of the acute stroke team; (d) training of staff working in the neuro-observation unit on how to administer rt-PA; and (e) development of a daily TIA clinic. In this observational study, of the 1127 patients admitted with stroke, 2.6% received rt-PA. Throughout the study period, there were significant reductions in mean delay from symptom onset to hospital arrival (63 to 49 min), from symptom onset to CT scanning (113 to 90 min), and from symptom onset to start of rt-PA (168 to 147 min).[25]

Discussion

Interventions to improve the efficiency of acute medical services are difficult to assess by means of conventional parallel group RCTs. We were therefore not surprised by the failure to identify any RCTs in this review. Non-randomized studies are subject to bias, hence any conclusions about observed changes may be less reliable. We therefore sought to at least describe the types of interventions and provide a qualitative description of their putative effects. The heterogeneity of study designs precluded a formal meta-analysis.

Public educational campaigns

The public needs to know the symptoms of a stroke, and that urgent medical care should be sought if they are to have a chance to receive rt-PA within 3 h of onset.[11] Two studies have demonstrated that public education campaigns through mass media could increase the public's knowledge of stroke symptoms and their risk factors, but did not assess the effects on delay to hospital arrival or use of rt-PA.[29,30] In this review, we found four studies that involved not only education of the public, but also training of the paramedical staff, primary care physicians, and ED staff. This type of combined educational programme appeared to have some effect in reducing the delay to receiving thrombolysis, increasing the use of emergency ambulances, and increasing the proportion of patients receiving rt-PA. However, it remains unclear how intensive such campaigns should be and how frequently they should be repeated.

Paramedical staff training

A significant proportion of stroke patients are admitted within 3 h of stroke onset. An audit of 739 patients from 22 hospitals in the UK found that 37% of patients arrived within 3 h; this figure is similar to that found in other parts of Europe, the US, and China.[14,31,32] To maximize the proportion of patients receiving rt-PA within 3 h, paramedical staff must be accurate in their diagnosis of stroke, so that those who might be eligible for thrombolysis can be transferred immediately to the appropriate stroke centre, whereas those with non-strokes (e.g. seizures, hypoglycaemia) are managed in the usual way. Various stroke assessment tools and training programmes have been shown to have a positive impact on the accuracy of pre-hospital

diagnosis of stroke.[3,33–35] Moreover, the studies included in this review found that training of paramedical staff could improve the speed of hospital admission. In the future, pre-hospital stroke care might even involve administration of a neuroprotective agent by paramedical staff.[3]

Implications for practice

We have identified several types of interventions that might speed up the delivery of thrombolysis for acute stroke. Although rt-PA should be administered speedily, the emergency physicians or stroke team must also follow strict guidelines if it is to be administered safely and adverse events are to be minimized.[36,37] Moreover, as patients with possible stroke arrive at the hospital earlier, the emergency physicians should be aware of the increased chance of the diagnosis being a TIA, intracerebral haemorrhage, or non-stroke condition.[38] Although many patients arriving early may not qualify to receive thrombolysis, at least they will be promptly admitted to an acute stroke unit for early physiological monitoring and multidisciplinary care.

The observed effects of each intervention are specific to the local organizational setting, so that it may not be applicable to every hospital or community. For instance, immediate assessment by the stroke team may not influence the use of thrombolysis if there is substantial delay to CT scanning.[39] We found that multifaceted programmes might have greater effects than single interventions, but such programmes may also require substantial resources and effort to execute and their cost-effectiveness is unproven.

This review did not find enough evidence to advocate one single intervention that is most likely to increase access to, and usage of, thrombolytic therapy for acute stroke. However, it has identified several approaches which might be tailored to suit local circumstances and available resources.

Implications for research

Further research is needed to identify cost-effective strategies to make the process of diagnosing and treating patients with suspected acute stroke faster and more efficient.

Acknowledgements

The authors are grateful to the Cochrane Stroke Group Editorial Base in Edinburgh, UK, for their assistance in designing and conducting the literature searches. The review was supported in part by a grant from the NHS Health Technology Assessment (HTA) Programme (Grant 98/02/02). The opinions and views expressed do not necessarily reflect those of the NHS Executive. The source of funding had no role in review design, data collection, data analysis, writing of the report, or decision to submit the paper for publication.

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