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A systematic review of barriers to delivery of thrombolysis for acute stroke

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Abstract

Background and purpose: barriers within the patient pathway can prevent early administration of thrombolytic therapy in patients admitted with acute stroke. This systematic review aimed to identify such barriers that have been reported in the medical literature.
Methods: we searched MEDLINE and EMBASE for prospective and retrospective observational studies that assessed the nature of barriers to delivery of thrombolysis for acute stroke.
Results: we identified 54 eligible studies (including a total of 39,030 patients). The reported barriers included: (i) the patient or family did not recognise symptoms of stroke or seek urgent help, (ii) the general practitioner (rather than an ambulance) was called first, (iii) the paramedics and emergency department staff triaged stroke as non-urgent, (iv) delays in neuroimaging, (v) inefficient process of in-hospital emergency stroke care, (vi) difficulties in obtaining consent for thrombolysis, and (vii) physicians' uncertainty about administering thrombolysis.
Conclusions: we identified important pre-hospital and in-hospital barriers that should be overcome if thrombolysis is to be administered to stroke patients efficiently and equitably.

Keywords: *stroke, hospitalisation, medical systems, hospital, thrombolytic therapy, CVA*

Introduction

Animal studies showed that the earlier acute treatments can be given to stroke victims, the more effective they may be [1]. This led to the concept of 'time is brain'. For ischaemic stroke, therefore, the main objective of treatment is to restore blood flow as soon as possible after arterial occlusion [2]. For some patients, the benefits of thrombolysis using recombinant tissue plasminogen activator (rt-PA) within 3 hours of onset may be substantial [3]. Alteplase, a form of rt-PA, has recently been given a limited European license to be used for treatment of acute ischaemic stroke within 3 hours of onset.

In a recent observational study of 739 stroke patients in 22 hospitals across the UK, as many as 37% of all patients arrived at the hospital within 3 hours of symptom onset [4]. This figure is comparable to those reported by studies from other countries [5–7]. However, due to delays along the patient pathway, only a small proportion of stroke patients actually receive thrombolytic therapy [8, 9]. Thrombolysis could therefore only be routinely administered if specific barriers are identified and successfully overcome. This systematic review – part of an NHS Health Technology Assessment (HTA) Project on acute stroke care [10] – aimed to describe such barriers that have been reported in the medical literature.

Methods

The details of the methods have been reported in full elsewhere [10]. In summary, we sought prospective and retrospective observational studies that assessed the nature or duration of barriers to thrombolysis for acute stroke. We excluded the following types of publications: (i) those that were not original research, (ii) studies that observed only

those patients who received rt-PA, (iii) surveys of opinions, and (iv) studies of very specialised groups of stroke patients.

We searched MEDLINE and EMBASE from 1990 to early 2001. The detailed version of the search strategy is available in the original NHS HTA report [10]. 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.

Results

We scanned 18,561 titles and abstracts and retrieved 112 publications in full text. From these, we included 54 studies that reported data on barriers to delivery of thrombolysis for acute stroke. In general, these studies covered one or more of three areas: (i) delays in the patient pathway, (ii) specific barriers to delivery of thrombolysis, and (iii) proportion of patients who were eligible for thrombolysis.

Quality of the studies

We found 54 observational studies (with 39,030 patients). Fifteen studies stated that patients were consecutively recruited [11–25]. Three studies recruited only patients with ischaemic strokes [8, 26, 27] and one study recruited only patients with first-ever strokes [28]. Fifty-two studies were hospital based and two studies were community based [21, 29]. Twenty-three studies were conducted in the USA or Canada, 20 in Europe (of which five were in the UK), six in Asia, two in Israel, two in Australia or New Zealand, and one in South America.

Delays in the patient pathway

Detailed results of the included studies are reported as supplementary data (available at http://www.ageing.oupjournals.org). In summary, the reported in-hospital delays included: (i) from stroke onset to arrival at hospital, and (ii) from arrival at hospital to first medical assessment, CT brain scan, neurologist assessment, ward admission and administration of thrombolysis.

Nine studies reported mean delay time from stroke onset to arrival at hospital [19, 20, 30–36]. The majority of the reported mean delays were between 2 and 6 hours but these varied widely, ranging from 1.9 ± 1.3 hours (mean $\pm$ standard deviation, SD) [30] to 12.2 ± 2 hours [19] to 29 ± 53.8 hours [20]. Eight studies reported mean delay time from arrival at hospital to CT scan [26, 27, 30, 32–34, 37, 38]. The majority of the reported mean delays were between 20 minutes and four hours but these again varied widely, ranging from 0.3 ± 0.3 hours [33] to 15.1 hours (no SD) [37] to 58 ± 41 hours [26].

Twenty-nine studies reported the proportions of patients arriving at hospital within various timeframes (see Table 1) [5–7, 11, 14, 17–22, 25, 27–29, 31, 32, 34, 35, 39–48]. In the UK, the proportion of patients arriving within 3 hours of stroke onset ranged from 25% [48] to 31% [40], which is comparable to the more recently published findings of Harraf *et al.* [4]. In the USA, where Alteplase has been licensed for use in acute stroke since 1995, this proportion appears to be larger, ranging from 30% [6] to 56% [34].

Specific barriers to delivery of thrombolysis for acute stroke

Detailed results of the studies are reported as supplementary data. In summary, we identified the following nine types of barriers.

(i) *The patient or family did not recognise symptoms of stroke or seek urgent help*: Twenty-one studies identified this as a barrier [6, 11, 13, 16–18, 20, 23, 31–33, 35, 36, 40, 42–46, 49, 50]. The commonest factors associated with it were: (i) patient living alone or was retired [11, 20, 31, 42, 45, 49], (ii) symptoms not recognised or not interpreted as stroke [13, 20, 35, 43, 44, 46], (iii) lack of bystander witness when stroke symptoms occurred [13, 16, 32, 49], (iv) patient or family not seeking medical help at all [6, 18, 23], (v) patient or family having no sense of urgency to seek help when symptoms started [20, 23, 33, 36, 43, 49], (vi) stroke symptoms started at home [40], and (vii) patient refused to go to hospital [20].

(ii) *Patient or family did not call an ambulance*: Twenty-three studies identified this as a barrier [6, 14, 16, 18, 20–23, 27, 28, 32–34, 36, 40, 42, 43, 46, 48–52]. These studies found that ambulance transfer was associated with a shorter delay to arrival at hospital, whereas first contacting a general practitioner (GP) increased the delay. One study observed that four groups of patients were particularly likely to arrive by ambulance: (a) patients living with someone else, (b) if a witness was present at stroke onset, (c) older patients, and (d) patients with haemorrhagic strokes [49]. Fourteen studies reported the proportion of patients who arrived by ambulance [6, 14, 16, 20, 22, 23, 36–38, 40, 47, 50, 52, 53]. This was generally about 50%, ranging from 38% [52] to 65% [14].

(iii) *Paramedical staff did not triage stroke as an emergency*: We found seven studies that evaluated delays from calling the emergency services to the time of ambulance arrival, and from ambulance arrival at the patient to reaching the hospital [6, 18, 20, 40, 47, 48, 54]. These studies found that stroke was often not regarded as an emergency by the paramedical staff, leading to slower ambulance transfer.

(iv) *Emergency department did not triage stroke as an emergency*: We found 27 studies that examined delay from stroke onset (or arrival at hospital) to first medical assessment, neurologist's assessment, or alerting the acute stroke team [6, 12–14, 16, 18, 20, 23, 26, 30, 32–34, 37–40, 42, 44, 47–49, 51, 54–57]. The median delay from arrival at hospital to first medical assessment varied considerably, ranging from 20 minutes [49] to 4 hours [13].

(v) *Delay in neuroimaging*: We found 22 studies that evaluated delay from stroke onset (or arrival at hospital) to the first CT scan [6, 7, 12, 16, 18–20, 22, 26, 27, 29, 30, 32–34, 37–39, 45, 48, 54, 56]. Delays occurred in: requesting the scan, transporting the patient to the radiology department, carrying

Table 1. Delay from stroke onset to arriving at hospital: proportions of patients arriving within 3 and 6 hours (studies are grouped according to continent and country)

Study	Continent	Country	% of patients arriving <3 h	% of patients arriving <6 h
Liu *et al.* 1995 [25]	Asia	China	50	65
Wang *et al.* 1997 [7]	Asia	China	24	35
Kay *et al.* 1992 [45]	Asia	Hong Kong	–	– (63 <12 h)
Siu *et al.* 1999 [18]	Asia	Hong Kong	52	–
Yoneda *et al.* 2000 [27]	Asia	Japan	34	–
Charleston *et al.* 1999 [39]	Australia/NZ	Australia	52	64
Anderson *et al.* 1995 [29]	Australia/NZ	New Zealand	– (52 <4 h)	–
Jorgensen *et al.* 1996 [11]	Europe	Denmark	– (25 <3.5 h)	35
Rasmussen *et al.* 2000 [21]	Europe	Denmark	38	53
Fogelholm *et al.* 1996 [28]	Europe	Finland	–	43
Lannehoa *et al.* 1999 [32]	Europe	France	60	77
Collins *et al.* 1999 [19]	Europe	Ireland	25	–
Azzimondi *et al.* 1997 [5]	Europe	Italy	43	56
Pistollato *et al.* 1996 [35]	Europe	Italy	61	80
Casetta *et al.* 1999 [31]	Europe	Italy	– (41 <2 h)	54 (<4 h)
Fiorelli *et al.* 1999 [22]	Europe	Italy	34	54
Ferro *et al.* 1994 [20]	Europe	Portugal	–	42
Harper *et al.* 1992 [42]	Europe	UK	27	49
Salisbury *et al.* 1998 [40]	Europe	UK	31	46
Johnston *et al.* 1999 [48]	Europe	UK	25	47
Streifler *et al.* 1998 [17]	Israel	Israel	26	54
Alberts *et al.* 1990 [43]	USA/Canada	USA	–	– (42 <24 h)
Biller *et al.* 1993 [44]	USA/Canada	USA	53	63
Smith *et al.* 1998 [41]	USA/Canada	USA	50	66
Kothari *et al.* 1999 [6]	USA/Canada	USA	30	40
Morris *et al.* 2000 [34]	USA/Canada	USA	56	–
Engelstein *et al.* 2000 [47]	USA/Canada	USA	– (6.5 <2 h)	–
Duncan *et al.* 2000 [46]	USA/Canada	USA	50	65
Lacy *et al.* 2001 [14]	USA/Canada	USA	46	61

out the scan, and reporting the scan by a neuroradiologist [12, 54].

(vi) *Inefficient process of in-hospital emergency stroke care*: We found 18 studies that evaluated delay from stroke onset (or arrival at hospital) to first medical assessment, neurologist's assessment, or ward transfer [6, 13, 16, 18, 20, 26, 30, 34, 37–39, 44, 48, 49, 51, 54–56]. Reported reasons for delay in ward transfer included beds being unavailable and delay in obtaining a porter to transport the patient [56].

(vii) *Difficulties in obtaining informed consent for thrombolysis*: In the acute phase, many stroke patients have language impairment or reduced consciousness, which makes it difficult to get their consent for treatment. Two studies identified this barrier. In one study, 10% of patients did not receive the treatment because they refused consent [56], whereas only 0.4% of patients refused in another study [24].

(viii) *Physicians' uncertainty in administering rt-PA*: In the USA, where rt-PA is licensed, one study in 1998 found that only 16% of neurologists had ever administered the treatment [58]. In this review, one study showed that some physicians were reluctant to administer rt-PA because of conflicting trial results and difficulty in starting treatment within 3 hours of stroke onset [39]. Another study found that some physicians were uncertain of the diagnosis of acute stroke in some patients, and this uncertainty led to delayed treatments [48].

(ix) *Other identified barriers*: Five studies reported other barriers: (a) delays in retrieving old medical records, performing phlebotomy, and acquiring the drug from pharmacy [12], (b) delays in transferring the patient from another hospital [26], (c) inadequate training in stroke for doctors [48], and (d) low accuracy of stroke diagnosis by paramedical staff [59, 60].

Proportion of stroke patients eligible for thrombolysis

Nine studies assessed the proportion of stroke patients who were potentially or actually eligible for thrombolytic therapy with rt-PA within 3 hours of stroke onset (see Table 2) [8, 9, 19, 22, 24, 27, 47, 56, 61]. One other study assessed the proportion of patients eligible for streptokinase therapy within 6 hours of onset [54]. The proportion varied widely, ranging from 0% [47] to 22% [24]. The five commonest reasons for being ineligible for rt-PA are summarised in Table 3.

Discussion

Methodological aspects

The identified studies were variable in quality, sample size, and study population. Many had substantial methodological weaknesses and were open to bias, precluding a meaningful quantitative meta-analysis of either the frequency or impact

Table 2. Proportions of stroke patients who were potentially or actually eligible for thrombolytic therapy with rt-PA within 3 hours of onset (studies are grouped according to continent and country)

Study	Continent	Country	% eligible
Yoneda *et al.* 2000 [27]	Asia	Japan	9
Grond *et al.* 1998 [24]	Europe	Germany	22
Collins *et al.* 1999 [19]	Europe	Ireland	6
Fiorelli *et al.* 1999 [22]	Europe	Italy	14
Andre *et al.* 1998 [56]	S. America	Brazil	9
Zweifler *et al.* 1998 [9]	USA/Canada	USA	3.7
Chiu *et al.* 1998 [61]	USA/Canada	USA	3
O'Connor *et al.* 1999 [8]	USA/Canada	USA	2.8
Engelstein *et al.* 2000 [47]	USA/Canada	USA	0

Table 3. Commonest reasons for being ineligible for thrombolysis using rt-PA, and the proportions of patients who were ineligible for these reasons

Reason for being ineligible for rt-PA therapy	Proportion (% range)
Delay to treatment >3 hours, or onset time unknown	22–94
CT scan shows haemorrhage or signs of extensive infarction	10–22
Clinical signs of stroke too mild or resolving rapidly	9–19
Medical contraindications to rt-PA	6–10
Refusal to consent to treatment	0.4–10

of specific barriers [62]. Summation of such confounded data would lead to unreliable aggregate results that are difficult to interpret and unable to influence one's practice. However, there was at least consistency in the reporting of the key barriers across a variety of healthcare settings. It is worth noting that although 39 of the 54 included studies did not recruit consecutive stroke patients, there was no apparent difference in the findings of these studies compared to the 15 studies that recruited consecutive patients. This may be because the majority of the studies recruited large numbers (hundreds) of patients and random errors might be minimised.

This systematic review was conducted in early 2001 and the search has been updated in 2003. The latest search has identified a further 32 studies of barriers to delivery of thrombolysis. We have not presented the results of these studies in this report because they are generally in line with those summarised here (references of these studies are available from the authors).

Pre-hospital barriers

The most consistently reported pre-hospital barrier was the patient's or family's poor knowledge of stroke which delayed their request for urgent medical help. Surveys have shown that many people do not know the presenting symptoms of stroke [63–65]. Even with adequate knowledge, the public has to be convinced that the emergency services, and not the GP, should be called when a person is suspected to have a brain attack. In the UK, where the majority of the hospitals do not provide a routine thrombolysis service for acute stroke, many patients are transported to the hospital early but not immediately [4]. The many barriers identified in this review, combined with the imprecision of the magnitude of risks and benefits with rt-PA treatment, may further hinder the widespread introduction of thrombolysis despite the newly granted license of Alteplase.

In-hospital barriers

The most common and consistently reported sources of delay were in: (i) medical assessment, (ii) neuroimaging, and (iii) transferring the patient to the ward. Measures to overcome these in-hospital barriers could include, e.g. training of emergency department staff to triage stroke as an emergency, improving access to CT scanning and training of stroke unit staff in administering thrombolysis.

Although many stroke patients arrive in the hospital within 3 hours of onset [4], unless they are triaged as high priority to be assessed and managed quickly, thrombolysis is unlikely to have a major impact on outcome [66]. Specific interventions, such as those designed to reduce the time to alerting the acute stroke team and transferring the patient to the neuroradiology department, might increase the use of thrombolysis [67].

In conclusion, this report provides a useful checklist of potential barriers to delivery of thrombolysis for acute stroke. These barriers could be assessed in future audits of local stroke services. Further research is needed to find the best methods of reorganising emergency stroke care so that thrombolysis could be administered effectively, efficiently and equitably.

Key points

- The benefits of thrombolysis using intravenous recombinant tissue plasminogen activator (rt-PA) within 3 hours of onset of stroke can be substantial.
- Barriers within the patient pathway can prevent the early administration of rt-PA.
- This systematic review has identified important pre-hospital and in-hospital barriers that should be overcome if thrombolysis is to be delivered effectively, efficiently and equitably.

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Possible conflicts of interest

The opinions and views expressed do not necessarily reflect those of the NHS Executive. Potential conflict of interest: Professor Peter Sandercock: (1) is a Co-principal Investigator

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