Q J Med 2006; **99**:625–633
doi:10.1093/qjmed/hcl082

Early neurological deterioration in acute stroke: clinical characteristics and impact on outcome

J. KWAN[1] and P. HAND[2]

From the [1]*Elderly Care Research Unit, Southampton General Hospital, Southampton, UK and* [2]*Department of Neurology, Royal Melbourne Hospital, Parkville, Australia*

Received 10 January 2006 and in revised form 15 May 2006

Summary

Background: A significant proportion of acute stroke patients suffer neurological deterioration during the first few days of recovery.
Aim: To explore the frequency, clinical characteristics, and consequences of early neurological deterioration during the acute recovery period.
Methods: We assessed all consecutive patients admitted to a University hospital with suspected stroke. We recorded the following on admission: baseline characteristics, physiological parameters and laboratory results. On day 5 we recorded occurrence of complications, and functional outcome. Early neurological deterioration was defined as an increase in National Institute of Health Stroke Score (NIHSS) by two or more points (or stroke-related death) between admission and day 5.
Results: We recruited 188 stroke patients, of whom 36 (19%) suffered early neurological deterioration. Patients with early neurological deterioration were significantly more likely to: (i) arrive at the hospital earlier (median 2.25 vs. 7.2 h, $p = 0.015$); (ii) have a history of atrial fibrillation (33% vs. 16%, $p = 0.039$); (iii) be current non-smokers (24% vs. 11%, $p = 0.041$); (iv) have a severe stroke—more total anterior circulation strokes (67% vs. 26%, $p < 0.001$) and worse NIHSS and GCS scores; (v) have intracerebral haemorrhage (22% vs. 7%, $p = 0.011$); (vi) have higher serum urea (mean 7.8 vs. 6.5 mmol/l, $p = 0.035$) and leukocyte count (mean 12.6 vs. 9.7×10^9/l, $p = 0.044$); and (vi) die in hospital (44% vs. 10%, OR 12.8, 95%CI 3.8–43.1, $p < 0.001$).
Discussion: Early neurological deterioration is a frequent and important complication in acute stroke, with a poor short-term prognosis. Effective treatment strategies are urgently needed to reduce its occurrence and impact on recovery.

Introduction

In acute stroke, the fate of the ischaemic penumbra directly depends on the severity and duration of ischaemia.[1] During this potentially unstable period, physiological factors such as homeostatic disturbances (e.g. hyperglycaemia, pyrexia) and haemostatic activation (e.g. excessive thrombin generation, fibrin turnover) can exacerbate neuronal death.[2–4] Early neurological deterioration within the first few hours or days of stroke onset has been variously termed 'stroke progression', 'early stroke progression', 'stroke-in-progression', and 'stroke-in-evolution'.[5] It is probably caused by a combination of pathophysiological mechanisms, including extension of the original infarction or haemorrhage, acute local recurrence, new but remote brain damage, systemic insults (e.g. severe inflammatory response from sepsis), brain oedema, hydrocephalus, and others.[6,7] In one recent study,

Address correspondence to Dr J. Kwan, Elderly Care Research Unit, Level E (807), Centre Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD. email: drjkwan@aol.com

a high concentration of glutamate (an excitatory amino acid involved in the ischaemic cascade) in the cerebrospinal fluid (CSF) was associated with neurological deterioration during the acute recovery phase of cerebral infarction.[8] A related study also found possible interactions between CSF glutamate level and pyrexia in patients with early neurological deterioration, raising the possibility that excitotoxicity and pyrexia could synergistically aggravate ischaemic damage and cell death.[9] Several studies have confirmed that early neurological deterioration is strongly correlated with poor functional outcome.[6,10,11]

Early neurological deterioration is common, occurring in 26–43% of patients, and about half of all cases occur within 24 h of admission.[11–14] Such wide variations in the observed prevalence may be due to selection bias and the use of different diagnostic criteria for in different studies; for example, a deleterious change of at least one point in the Canadian Neurological Scale (CNS), or at least two points in the Scandinavian Stroke Scale (SSS) or the NIH Stroke Scale (NIHSS).[6,12–15] These diagnostic criteria also vary in their timeframe, which could also affect the apparent frequency. For instance, the longer the period between assessments, the more likely it is that the patient will deteriorate, simply because the period of observation is longer. On the other hand, the patient will have more time to improve from the episode, and thus may not be identified as having persistent neurological deterioration. More recently, the European Progressing Stroke Study Group has attempted to standardize the diagnostic criteria, and studied in detail the validity and reliability of one particular definition of early neurological deterioration: namely, a reduction of at least two points in the SSS in either conscious level, arm, leg or eye movement score, and/or a reduction of at least three points in SSS in speech score, between baseline and day 3.[16] This study found that, as compared to another definition using changes in CNS, the European Progressing Stroke Study's definition had reasonable validity and was predictive of functional outcome at 3 months.[16] As yet, there is still no international consensus and different variations of this definition have been used in recent studies.[3,4]

In this prospective study, we sought to examine in detail the clinical characteristics of the patients who develop early neurological deterioration within the first 5 days after admission, its frequency of occurrence, associated risk factors, and influences on functional outcome.

Methods

Subjects

We assessed all consecutive patients who presented to our University hospital with suspected stroke between July 2000 and April 2001. Several overlapping methods of case ascertainment were used to ensure completeness of recruitment, including the emergency department admission record, information given by the emergency department nurses and doctors who altered the research team, the consultants in charge of the acute stroke unit, and the daily neuroimaging meeting in the department. Patients were included if they were admitted with confirmed stroke or transient ischaemic attack (TIA), and excluded if they were subsequently found to have a non-stroke condition (e.g. brain tumour, hypoglycaemia, and epilepsy); patients with a diagnosis of subarachnoid haemorrhage on neuroimaging were also excluded since they were generally admitted and managed by the neurosurgical team.

Study protocol

Each patient was assessed on the day of admission (or the next working day if admitted during the weekend) and again on day 5 after admission (or the next working day if this was during the weekend), if the patient was still in hospital. We did not record the exact timing of each assessment, but the vast majority were conducted within 24 h (of admission or day 5). On admission, the research team recorded data related to the patients' baseline and clinical characteristics including stroke severity, physiological parameters, and laboratory results. On day 5, we recorded data on stroke severity, the occurrence of neurological sequelae and complications, process of care, and functional outcome between the initial assessment and follow-up. The destination and date of discharge, and in-hospital deaths, were extracted from case notes after the patient had been discharged or had died. The National Institute of Health Stroke Score (NIHSS) and Glasgow Coma Score (GCS) were used to assess stroke severity (all researchers were trained and certified in administering the NIHSS).[17,18] Stroke syndromes were clinically divided according to the Oxfordshire Community Stroke Project (OCSP) classification system.[19] In the present study, early neurological deterioration was defined as a change by at least two points in the NIHSS between admission and day 5. Similar to the European Progressing Stroke Study's definition, we also classified patients who died primarily of their stroke event within 5 days as early neurological deterioration; these patients

did not have a second NIHSS assessment by the research team on day 5. For this category, patients who died primarily of non-stroke conditions (e.g. systemic infection, acute coronary event) were excluded.

The research team had no direct involvement in the daily clinical care of these patients during the admission (except if they were eligible for thrombolysis: see below). The performance of investigations, management of abnormal physiological parameters, and initiation of treatments were the responsibilities of the admitting medical team. Intravenous thrombolysis (within 6 h of stroke onset) was available as part of the Third International Stroke Trial (IST-3, a randomized placebo-controlled trial of IV rt-PA for acute ischaemic stroke presenting within 6 h of onset, [http://www.ist3.com]), and patients were randomized into this trial if they satisfied the eligibility criteria. From the emergency department, all acute stroke patients were transferred to, and managed on, the acute stroke unit or general medical wards, according to local clinical guidelines. The nursing staff performed frequent non-invasive monitoring of blood pressure, temperature, heart rate, and pulse oximetry. A multidisciplinary team of therapists provided early rehabilitation (regardless of ward location), and some patients were transferred within a few days to other rehabilitation units according to clinical needs. Ethical approval was granted for the routine collection of prospective data on hospital referral cases to evaluate in-patient care and related observational studies, including the present one.

Statistical analysis

Results are expressed as means (SD) or medians (IQR) as appropriate, throughout the text and tables. For dichotomous outcomes, comparisons of proportions were performed using Yates-corrected χ^2 test or Fisher's exact test; odds ratios and 95%CIs were reported where appropriate. For outcomes with continuous data, comparisons were performed using Student's t-test or the Mann-Whitney U test, depending on the normality of data distribution. For analysis of functional outcomes that could be influenced by case mix and stroke severity, adjustments were made using multinomial logistic regression analysis; covariates used for adjustment included age, pre-stroke living status, NIHSS and GCS on admission, and OCSP subclass. All statistical analyses used SPSS for Windows (v. 12, SPSS, 2005).

Results

We included a total of 188 patients in the study, of whom 186 patients had strokes and two had TIAs. Thirty-six patients (19%) met the criteria for early neurological deterioration. Of these 36, 20 had NIHSS assessments at baseline and day 5, whereas 16 patients died before day 5 (and thus did not have the second assessment).

There were no significant differences in the mean age, gender distribution, pre-stroke level of independence and living status between those patients who suffered early neurological deterioration and those who did not (Table 1). However, there were significant differences in several items in the clinical history (Table 1). Patients with early neurological deterioration had significantly shorter delay from stroke onset to arrival at the hospital (median delay 2.25 vs. 7.2 h, $p=0.015$), and more patients with early neurological deterioration had a history of atrial fibrillation (33% vs. 16%, $p=0.039$), but fewer patients were current cigarette smokers (11% vs. 24%, $p=0.041$). However, there were no significant differences for other items in the clinical history (e.g. previous history of hypertension, coronary heart disease, stroke, diabetes mellitus, and use of antiplatelet agents pre-stroke) or physical examination (evidence of dysfunction of heart valves).

On admission, there were significant differences in the clinical characteristics of the stroke event (Table 2). Significantly more patients with early neurological deterioration presented with total anterior circulation strokes (TACS, 67% vs. 26%, $p<0.001$), and fewer patients with partial anterior circulation strokes (PACS, 8% vs. 35%, $p<0.001$) or posterior circulation strokes (POCS, 3% vs. 13%, $p=0.049$). Haemorrhagic stroke subtype was more prevalent in the early neurological deterioration group (22% vs. 7%, $p=0.011$). On admission, stroke severity was significantly higher in the early neurological deterioration group, in terms of baseline NIHSS (median score 20 vs. 5, $p<0.001$) and GCS (median score 9 vs. 15, $p<0.001$). Interestingly, patients with early neurological deterioration had lower mean body temperature on admission (mean temperature 35.9 vs. 36.4°C, $p<0.001$), but there were no significant differences in other physiological parameters on admission, including blood glucose, oxygen saturation, systolic blood pressure or diastolic blood pressure. Routine blood tests performed within 24 h of admission also revealed significant differences: patients with early neurological deterioration had higher mean levels of serum urea (mean 7.8 vs. 6.5 mmol/l, $p=0.035$) and leukocyte count

Table 1 Demographics and baseline characteristics of patients with and without early neurological deterioration (END)

	With END ($n=36$)	Without END ($n=152$)	p
Demographics (*number*, %)			
Age (years) (mean, SD)[a]	78.5 (10.8)	74.7 (12.5)	0.092
Male gender	17 (47%)	68 (45%)	0.934
Independent pre-stroke (mRS <3)	25 (69%)	94 (62%)	0.510
Living alone pre-stroke	12 (33%)	62 (41%)	0.526
Clinical assessment (*number*, %)			
Admission delay (h) (median, IQR)[b]	2.25 (1.5–10.1)	7.2 (2.7–24)	0.015*
Atrial fibrillation	12 (33%)	25 (16%)	0.039*
Hypertension	17 (47%)	75 (49%)	0.965
Coronary heart disease	10 (28%)	54 (36%)	0.492
Previous cerebrovascular event	7 (19%)	52 (34%)	0.129
Diabetes mellitus	3 (8%)	18 (12%)	0.209
Peripheral vascular disease	3 (8%)	16 (11%)	0.236
Current cigarette smoker	4 (11%)	37 (24%)	0.041*
Antiplatelet Rx pre-stroke	17 (47%)	79 (52%)	0.743
Antihypertensive Rx pre-stroke	14 (39%)	71 (47%)	0.508
Anticoagulant Rx pre-stroke	6 (17%)	26 (17%)	0.854
Valvular heart disease on exam	6 (17%)	21 (14%)	0.862

TIA, transient ischaemic attack; Rx, therapy; mRS, modified Rankin score (mRS score <3 indicates independence with activities of daily living). *$p<0.05$. [a]Student's *t*-test for comparing parametric data. [b]Mann-Whitney U-test for comparing non-parametric data.

(mean 12.6 vs. 9.7×10^9/l, $p=0.044$). In terms of neurological sequelae, patients with early neurological deterioration were more likely to experience dysphagia (86% vs. 37%, $p<0.001$), urinary incontinence (92% vs. 46%, $p<0.001$) or reduced level of consciousness (83% vs. 29%, $p<0.001$) within the first five days (Table 2).

Patients with early neurological deterioration were significantly more likely to be catheterized in the first five days (47% vs. 22%, $p=0.005$), but there was no significant difference in the occurrence of complications such as pneumonia, urinary tract infections and seizures (Table 3). After adjusting for case-mix, patients with early neurological deterioration were significantly more likely to die in hospital (44% vs. 10%, OR 12.8, 95%CI 3.8–43.1, $p<0.001$), and less likely to be discharged home (6% vs. 24%, OR 0.12, 95%CI 0.02–0.62, $p=0.011$), whereas there was no significant difference in the risk of institutionalization (19% vs. 24%, OR 0.55, 95%CI 0.21–1.41, $p=0.21$, see Table 3). If we only considered the discharge destinations for survivors, patients with early neurological deterioration were significantly less likely to be discharged home (OR 0.17, 95%CI 0.03–0.94, $p=0.042$) but more likely to be institutionalized (OR 5.82, 95%CI 1.06–31.87, $p=0.042$). Overall, length of stay in the acute hospital was significantly shorter in the early neurological deterioration group (median length of stay 9.5 vs. 12 days, $p=0.001$).

Discussion

In this prospective study, early neurological deterioration was common, occurring in ~1:5 stroke patients admitted to the hospital. This figure is similar to that of previously published studies of hospital cohorts.[11–14,20] In the recent European Study Progressing Stroke Study, preliminary results showed early neurological deterioration in 26% of patients within the first 3 days after acute stroke, whereas *any* early neurological worsening (transient or persistent for at least three days) occurred in 33% of patients.[16] Although similar, the frequency observed in our study was slightly lower than in previous studies (except in one study that found a rate of 9.8%). This could be because we used a slightly different definition of early neurological deterioration, and/or that the majority of patients suffered relatively mild strokes on admission (median NIHSS for the whole group was 5, IQR 3–11; median GCS was 15, IQR 9–15). The European Progressing Stroke Study also classified patients who died in the first three days as having early neurological deterioration, but they did not distinguish deaths that were primarily caused by the stroke event from those caused by other co-morbidities. In our study, we have separated these two groups and included only those whose primary cause of death was stroke. In the process, we have excluded eight patients who also died

Table 2 Clinical characteristics of the stroke event on admission, laboratory findings, and neurological sequelae, in patients with and without early neurological deterioration (END)

	With END ($n=36$)	Without END ($n=152$)	p
Stroke subtype (*number*, %)			
OCSP TACS	24 (67%)	39 (26%)	<0.001*
OCSP PACS	3 (8%)	53 (35%)	<0.001*
OCSP LACS	5 (14%)	35 (23%)	0.093
OCSP POCS	1 (3%)	20 (13%)	0.049*
OCSP undeterminable	3 (8%)	5 (3%)	0.136
Intracerebral haemorrhage	8 (22%)	10 (7%)	0.011*
Stroke severity (*median, IQR*)[a]			
NIH Stroke Score	20 (9–26.5)	5 (3–12)	<0.001*
Glasgow Coma Score	9 (2.3–13.5)	15 (9–15)	<0.001*
Physiological variables (*mean, SD*)[b]			
Temperature (°C)	35.9 (0.8)	36.4 (0.7)	<0.001*
Blood glucose (mmol/l)	6.5 (2.6)	6.9 (3.3)	0.618
Oxygen saturation (%)	96.8 (3.1)	95.9 (3.0)	0.114
Systolic BP (mmHg)	154.2 (35.7)	162.1 (29.9)	0.173
Diastolic BP (mmHg)	87.2 (20.1)	91.9 (18.4)	0.172
Laboratory findings (*mean, SD*)[b]			
Serum sodium (mmol/l)	140.7 (2.7)	140.7 (3.3)	0.975
Serum potassium (mmol/l)	4.2 (0.5)	4.3 (0.5)	0.311
Serum urea (mmol/l)	7.8 (4.6)	6.5 (3.0)	0.035*
Serum creatinine (mmol/l)	93.1 (33.8)	92 (42.6)	0.891
Haemoglobin (g/l)	131.4 (18.8)	137.7 (17.0)	0.052
Leukocyte count ($x10^9$/l)	12.6 (15.8)	9.7 (3.7)	0.044*
Platelet count ($x10^9$/l)	227.4 (70.3)	245.5 (75.7)	0.192
Neurological sequelae (*number*, %)			
Dysphagia	31 (86%)	56 (37%)	<0.001*
Urinary incontinence	33 (92%)	70 (46%)	<0.001*
Reduced consciousness	30 (83%)	44 (29%)	<0.001*

NIH, National Institute of Health; OCSP, Oxford community stroke project; TACS, total anterior circulation stroke; PACS, partial anterior circulation stroke; LACS, lacunar stroke; POCS, posterior circulation stroke. *$p<0.05$. [a]Mann-Whitney U-test for comparing non-parametric data. [b]Student's *t*-test for comparing parametric data.

within the first 5 days, but whose cause of death was not stroke (four died from pneumonia, two from myocardial infarction, one from acute bowel ischaemia, and one from an unknown but non-stroke condition). If these eight patients had also been included, the frequency of early neurological deterioration would have increased to 23%. In our study, since patients did not receive daily NIHSS assessments between admission and day 5, we were unable to determine the proportion of patients who suffered transient neurological worsening that occurred within the first five days (this was known as 'early deterioration episode' in the European Progressing Stroke Study), or the exact time delay from stroke onset to deterioration.[21]

We did not find any significant association between early neurological deterioration and the patient's age, gender, or pre-stroke level of independence. This is in contrast to the European Progressing Stroke Study[16] and Castillo *et al.*,[8] both of which found that older patients were significantly more likely to suffer early neurological deterioration. However, our study found an association with time delay from stroke onset to hospital arrival, history of atrial fibrillation, and cigarette smoking in the clinical history. Interestingly, Castillo *et al.*[8] also found an association with admission delay, but in that study, patients with early neurological deterioration had significantly longer delay (not shorter delay as observed in our study). In other studies, atrial fibrillation and headache at stroke onset were also correlated with early neurological deterioration.[3,21,22] Similarly, cardioembolic stroke subtype was a risk factor in Sumer *et al.*,[5] but other studies did not find such a correlation.[23]

Our patients with higher stroke severity were more likely to have early neurological deterioration. This is in agreement with most other studies,[3,8,16,21] but not all.[11] Our finding was consistent with NIHSS

Table 3 Process of care, occurrence of complications, length of stay, and functional outcome, in patients with and without early neurological deterioration (END)

	With END ($n=36$)	Without END ($n=152$)	p
Process of care (*number*, %)			
IV thrombolysis <6 h[a]	1 (3%)	4 (3%)	0.414
Urinary catheterization	17 (47%)	34 (22%)	0.005*
Parenteral feeding	2 (6%)	3 (2%)	0.195
Oral antibiotics	2 (6%)	19 (13%)	0.130
Intravenous antibiotics	10 (28%)	24 (16%)	0.150
Intravenous fluid therapy	21 (58%)	62 (41%)	0.086
Complications (*number*, %)			
Pneumonia	3 (18%)	23 (15%)	0.133
Urinary tract infection	3 (8%)	12 (8%)	0.260
Deep vein thrombosis/PE	0 (0%)	1 (0.7%)	NA
Pressure sore	1 (3%)	3 (2%)	0.410
Seizures	3 (8%)	8 (5%)	0.217
Any complication	25 (69%)	87 (57%)	0.249
Functional outcome (*number*, %)[c]			
Death in hospital	16 (44%)	15 (10%)	<0.001*
Discharge home (all patients)	2 (6%)	36 (24%)	0.011*
Discharge home (of survivors)	2/20 (10%)	36/137 (26%)	0.21
Institutionalization (all patients)	7 (19%)	36 (24%)	0.042*
Institutionalization (of survivors)	7/20 (35%)	36/137 (26%)	0.042*
Length of stay, days (median, IQR)[b]	9.5 (3–48.3)	12 (7–20)	0.001*

PE, pulmonary embolism. NA, not applicable (calculation of χ^2 was not possible with 0% as one of the data entries). *$p<0.05$. [a]Patients were randomized into Third International Stroke Trial (IST-3). [b]Mann-Whitney U-test for comparing non-parametric data. [c]Comparison of functional outcome has been adjusted for case-mix using a well-validated prognostic model (see Methods).

as well as GCS, and other studies using different stroke severity scales (e.g. CNS, SSS) have reported similar trends. This relationship with stroke severity is also supported by our finding that patients with TACS and cerebral haemorrhage were significantly more likely to have early neurological deterioration, as others have also found.[3,16] In the European Progressing Stroke Study, primary haemorrhage increased the odds of stroke progression by two-fold.[3,16] In another study, the size of cerebral infarction, as estimated from neuroimaging, was also correlated with stroke progression.[8] Not surprisingly, therefore, our patients with early neurological deterioration were more likely to experience neurological sequelae of severe stroke such as dysphagia, incontinence, and reduced consciousness. In our study, since the research team was not blinded to the baseline and clinical data on admission or day 5, it is possible that the recording of non-fatal outcomes might have been influenced by bias.

Serum urea level and leukocyte count was also higher amongst patients with early neurological deterioration, which suggests that it might induce a greater level of systemic inflammatory response, or lead to physiological sequelae including dehydration (e.g. reduced oral intake secondary to dysphagia and reduced consciousness). Another interpretation is that these physiological changes might themselves increase the likelihood of early neurological deterioration, as others have also suggested.[3,24] However, whether this association implies causation remains unclear and the underlying pathophysiological mechanism has not been elucidated. Interestingly, lower body temperature on admission was associated with early neurological deterioration, and this was also reported by the European Progressing Stroke Study.[16] However, another study found an association with elevated body temperature.[23] Previous studies have also found links with other physiological variables, including systolic blood pressure and diabetes mellitus.[13]

Importantly, we found that early neurological deterioration was predictive of poor functional outcome, which is independent of stroke severity and case mix. It greatly increased the odds of dying in hospital, and survivors at discharge were more likely to be institutionalized and less likely to be discharged home. In our patients, 44% of those with early neurological deterioration died in

hospital, and 35% of the survivors were institutionalized. These mortality rates are generally higher than those found in other such studies: one reported 19% at discharge and 24% at 6 months,[5] another reported 33% at 3 months.[3] In our study, an increased odds of in-hospital death might also have accounted for the shorter length of stay (by 2.5 days) in the acute hospital. However, early neurological deterioration does not always mean a poor prognosis. In a study of patients who had been given intravenous recombinant tissue plasminogen activator (rt-PA), one third of those who did not respond to treatment in the first 24 h (either with worsening or no change in their neurological status) still achieved good outcome at 3 months; the authors suggested the possibility of a 'stunned brain syndrome', which remains capable of slower recovery despite a poor initial response.[25,26]

In an era when thrombolysis is increasingly used for acute ischaemic stroke, physicians and patients are most worried about neurological worsening after the administration of the agent, which could theoretically be a result of secondary intracerebral haemorrhage or re-occlusion after an initial successful re-canalization. In clinical trials, symptomatic intracerebral haemorrhage occurred in 5.8% of patients who had been administered intravenous rt-PA within 3 h, equivalent to an OR of 3.4 (95%CI 1.5–7.8), with an extra 62 extra events per 1000 patients treated compared to placebo.[27] In the NINDS rt-PA Stroke Trial, around 13% of patients suffered clinical deterioration after initial improvement following intravenous rt-PA, but the authors did not find any correlation with arterial re-occlusion.[24] However, in another study, arterial re-occlusion occurred in 75% of patients who suffered early neurological deterioration after intravenous rt-PA, vs. 22% of those who clinically improved.[25,26] Certain physiological derangements such as hyperglycaemia have been found to be a risk factor for early neurological deterioration (within 24 h) in patients receiving intra-arterial thrombolysis.[20]

The process of secondary neuronal damage can occur very quickly after the initial stroke, and any attempts to halt the process should be made aggressively and urgently. Acute stroke unit care is increasingly characterized by intensive physiological monitoring and correction of abnormal parameters such as fever, hyperglycaemia, hypoxia, and dehydration.[28–30] Studies suggest that this 'intensive' style of stroke unit care could almost half the number of deaths within the first 3 weeks (from 14% to 8%), and it has been suggested that this could be a result of preventing early neurological deterioration.[28–30] One randomized trial found that intensive non-invasive physiological monitoring improved the rate of detection and correction of abnormal parameters, and significantly fewer patients in the intensive monitoring group had early neurological deterioration (OR 0.24, 95%CI 0.09–0.63).[31] One non-randomized trial also found that non-invasive physiological monitoring and correction of abnormal parameters improved outcome and reduced length of stay.[32] On the other hand, pharmacological treatment strategies designed to prevent early neurological deterioration (e.g. continuous intravenous heparin therapy for one week) have not been shown to be beneficial.[33]

Our study was limited by the moderate sample size and statistical power. The study population was based on hospital referrals, and hence the results cannot be generalized to the wider community: some cases might have been missed if they had never reached hospital, or if deterioration had occurred before arrival. Another limitation is that we did not assess functional outcome at a predetermined time after the stroke event (e.g. at 3 or 6 months). This may have confounded certain outcomes (e.g. occurrence of infections) which were affected by the length of stay. Due to the complexity of the pathophysiological process of acute stroke, we also could not entirely exclude the possibility of an incomplete adjustment of functional outcome for case mix and other factors; this could potentially influence the internal validity of the study. Other complications might possibly have gone unnoticed, such as clinically silent thrombo-embolism and infections, cerebral haemodynamic disturbances, and subtle physiological fluctuations. Although the detection of these complications might be important and potentially useful in exploring the aetiology of early neurological deterioration, it would have required much more extensive investigations. Moreover, since we did not routinely repeat the neuroimaging, certain cases of asymptomatic brain oedema and haemorrhagic transformation could have been missed. Future research should take these important factors into consideration.

Early neurological deterioration is one of the most important complications in acute stroke, and is associated with significant mortality and morbidity. Efforts should be made to develop treatments to reduce its frequency and its impact on recovery and outcome.

Acknowledgements

The study was conducted at the Department of Clinical Neurosciences, Western General Hospital, Edinburgh. The data were collected by JK and PH,

the data were analysed by JK, and both JK and PH contributed to the preparation of the manuscript. JK was funded by The Stroke Association and Glaxo Wellcome, and PH was funded by Chief Scientist Office, Health Department, Scottish Executive, grant reference CZB/4/14. Professors Peter Sandercock and Martin Dennis supervised the research and offered advice on the preparation of the manuscript.

References

1. Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. *Cerebrovasc Dis* 2001; **11(Suppl 8)**:2–8.
2. Greenberg JH. Glucose and oxygen metabolism in ischaemia. *Cerebrovascular Disease. Pathophysiology, diagnosis, and management*. Malden, Blackwell Science, 1998:227–48.
3. Barber M, Langhorne P, Rumley A, Lowe GD, Stott DJ. Hemostatic function and progressing ischemic stroke: D-dimer predicts early clinical progression. *Stroke* 2004; **35**:1421–5.
4. Busto R, Ginsberg MD. The influence of altered brain temperature in cerebral ischaemia. In: *Cerebrovascular Disease. Pathophysiology, diagnosis, and management*. Malden, Blackwell Science, 1998:287–307.
5. Sumer M, Ozdemir I, Erturk O. Progression in acute ischemic stroke: frequency, risk factors and prognosis. *J Clin Neurosci* 2003; **10**:177–80.
6. Castillo J. Deteriorating stroke: diagnostic criteria, predictors, mechanisms and treatment. *Cerebrovasc Dis* 1999; **9**:1–8.
7. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. The recombinant activated factor VII intracerebral hemorrhage trial investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; **352**:777–85.
8. Castillo J, Davalos A, Noya M. Progression of ischaemic stroke and excitotoxic aminoacids. *Lancet* 1997; **349**:79–83.
9. Castillo J, Davalos A, Noya M. Aggravation of acute ischemic stroke by hyperthermia is related to an excitotoxic mechanism. *Cerebrovasc Dis* 1999; **9**:22–7.
10. Jorgensen HS, Reith J, Nakayama H, Kammersgaard LP, Houth JG, Raaschou HO, Olsen TS. Potentially reversible factors during the very acute phase of stroke and their impact on the prognosis: is there a large therapeutic potential to be explored? *Cerebrovasc Dis* 2001; **11**:207–11.
11. Britton M, Roden A. Progression of stroke after arrival at hospital. *Stroke* 1985; **16**:629–32.
12. Davalos A, Cendra E, Teruel J, Martinez M, Genis D. Deteriorating ischemic stroke: risk factors and prognosis. *Neurology* 1990; **40**:1865–9.
13. Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Effect of blood pressure and diabetes on stroke in progression. *Lancet* 1994; **344**:156–9.
14. Toni D, Fiorelli M, Gentile M, Bastianello S, Sacchetti ML, Argentino C, Pozzilli C, Fieschi C. Progressing neurological deficit secondary to acute ischemic stroke. A study on predictability, pathogenesis, and prognosis. *Arch Neurol* 1995; **52**:670–5.
15. Davalos A, Toni D, Iweins F, Lesaffre E, Bastianello S, Castillo J. Neurological deterioration in acute ischemic stroke: potential predictors and associated factors in the European cooperative acute stroke study (ECASS) I. *Stroke* 1999; **30**:2631–6.
16. Birschel P, Ellul J, Barer D. Progressing stroke: towards an internationally agreed definition. *Cerebrovasc Dis* 2004; **17**:242–52.
17. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. *Arch Neurol* 1989; **46**:660–2.
18. Jennett B, Bond M. Assessment of outcome after severe brain damage: A practical scale. *Lancet* 1975; **7905**:480–4.
19. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991; **337**:1521–6.
20. Leigh R, Zaidat OO, Suri MF, Lynch G, Sundararajan S, Sunshine JL, Tarr R, Selman W, Landis DM, Suarez JI. Predictors of hyperacute clinical worsening in ischemic stroke patients receiving thrombolytic therapy. *Stroke* 2004; **35**:1903–7.
21. DeGraba TJ, Hallenbeck JM, Pettigrew KD, Dutka AJ, Kelly BJ. Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. *Stroke* 1999; **30**:1208–12.
22. Leira R, Davalos A, Aneiros A, Serena J, Pumar JM, Castillo J. Headache as a surrogate marker of the molecular mechanisms implicated in progressing stroke. *Cephalalgia* 2002; **22**:303–8.
23. Audebert HJ, Pellkofer TS, Wimmer ML, Haberl RL. Progression in lacunar stroke is related to elevated acute phase parameters. *Eur Neurol* 2004; **51**:125–31.
24. Grotta JC, Welch KMA, Fagan SC, Lu M, Frankel MR, Brott T, Levine SR, Lyden PD. Clinical deterioration following improvement in the NINDS rt-PA stroke trial. *Stroke* 2001; **32**:661–8.
25. Alexandrov AV, Hall CE, Labiche LA, Wojner AW, Grotta JC. Ischemic stunning of the brain: early recanalization without immediate clinical improvement in acute ischemic stroke. *Stroke* 2004; **35**:449–52.
26. Alexandrov AV, Felberg RA, Demchuk AM, Christou I, Burgin WS, Malkoff M, Wojner AW, Grotta JC. Deterioration following spontaneous improvement: sonographic findings in patients with acutely resolving symptoms of cerebral ischemia. *Stroke* 2000; **31**:915–9.
27. Wardlaw JM, del Zoppo G, Maguchi T. Thrombolysis for acute ischaemic stroke (Cochrane systematic review). In: *The Cochrane Library, Issue* 1, 2002. Oxford, Update Software.
28. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Haheim LL. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important?. *Stroke* 1999; **30**:917–23.
29. Ronning OM, Guldvog B. Stroke unit versus general medical wards, II: neurological deficits and activities of daily living: a quasi-randomized controlled trial. *Stroke* 1998; **29**:586–90.

30. Ronning OM, Guldvog B. Stroke units versus general medical wards, I: twelve- and eighteen-month survival: a randomized, controlled trial. *Stroke* 1998; **29**:58–62.

31. Davis M, Hollyman C, McGiven M, Chambers I, Egbuji J, Barer D. Physiological monitoring in acute stroke. *Age Ageing* 1999; **28**:45.

32. Cavallini A, Micieli G, Zambrelli E, Quaglini S, Rognoni C. Role of continuous physiological monitoring in the acute phase of stroke [Abstract]. *Cerebrovasc Dis* 2001; **11**:117.

33. Duke RJ, Bloch RF, Turpie AG, Trebilcock R, Bayer N. Intravenous heparin for the prevention of stroke progression in acute partial stable stroke. *Ann Intern Med* 1986; **105**:825–8.