Thrombolytic therapy for acute stroke in the United Kingdom: experience from the safe implementation of thrombolysis in stroke (SITS) register

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Received 20 June 2008 and in revised form 14 July 2008

Summary

Aim: To describe the United Kingdom (UK) experience with thrombolytic therapy with intravenous alteplase (rt-PA) for stroke, as captured by the Implementation of Thrombolysis in Stroke (SITS) project.

Methods: The multinational Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was an observational study to assess the safety and efficacy of thrombolytic therapy, when administered within the first 3 h after onset of ischaemic stroke. SITS-MOST was embedded within the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), an internet-based, international monitoring registry for auditing the safety and efficacy of routine therapeutic use of thrombolysis in acute ischaemic stroke. We performed an analysis of data contributed to SITS-MOST and SITS-ISTR from UK centres.

Results: A total of 614 patients received thrombolysis for stroke between December 2002 and April 2006, 327 were registered to SITS-MOST and 287 to SITS-ISTR. Thirty-one centres treated patients in the UK, of which 23 registered patients in both SITS-MOST and SITS-ISTR and eight solely to SITS-ISTR. The median age from the UK SITS-MOST was identical to the non-UK SITS-MOST register: 68 years (IQR 59–75). The majority (96.1%) of patients from the UK were treated between 8.00 a.m. and 9.00 p.m., and only 18.4% were treated on weekend days, reflecting the difficulties of maintaining provision of a thrombolytic service out of hours. Median onset-to-treatment-time was 155 min (IQR 130–170 min) for the UK, compared to 140 min (IQR 114–165 min) for the non-UK SITS-MOST group (P < 0.001). UK SITS-MOST patients at baseline had more severe stroke in comparison with non-UK patients [median NIHSS 14.5 (IQR 9–19) vs. 12 (IQR 8–17) (P < 0.001)]. Forty-eight percent of UK patients achieved mRS of 0–2 (independence), compared to 55% of the non-UK SITS-MOST register. There was no significant difference in symptomatic intracerebral haemorrhage rate in the UK compared with the non-UK SITS-MOST patients [2.5% (95% CI 1.3–4.8) vs. 1.7% (95% CI 1.4–2.0) P = 0.28]. In the multivariate analysis, there was no statistically significant difference in any outcome between UK and non-UK SITS-MOST patients.
Conclusion: Thrombolytic therapy for stroke has been implemented successfully at a small number of UK stroke centres, with patchy provision throughout the country. The low frequency of treatment outwith office hours suggests deficient infrastructure to support delivery. UK patients tended to be more severely affected at baseline and to be treated later. Outcomes are comparable to those seen at the non-UK SITS centres.

Introduction

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) has confirmed the safety and effectiveness of recombinant tissue plasminogen activator (rt-PA) when used for the treatment of acute ischaemic stroke within Europe. The United Kingdom (UK) in general and Scotland in particular have generous time windows for routine brain imaging written into national guidelines produced by expert groups. Fewer than half of all UK stroke patients undergo brain imaging within 24 h of symptom onset. The UK has poor outcomes for stroke in comparison to other countries. Deficiencies in the recognition of the symptoms of stroke, coordination between ambulance services and stroke teams, availability of specialised acute stroke care and imaging in the UK have been acknowledged, and the initial slow uptake of thrombolytic therapy for stroke within the UK raises the question of whether widespread implementation of thrombolysis in the UK will be feasible, sustainable and safe. This question is made more pressing by the recent favourable cost-effectiveness assessment of thrombolysis of ischaemic stroke performed by the National Institute for Health and Clinical Excellence. We report the UK experience of thrombolysis for stroke between December 2002 and April 2006 as recorded in the SITS-MOST register. We also present the data from those patients treated outwith the restrictions imposed by the SITS-MOST study and captured in the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) between May 2002 and October 2006.

Methods

Detailed descriptions of the SITS-MOST study design, methodology, data management and results exist elsewhere. Briefly, SITS-MOST was an open, multinational, prospective observational study, which collected data from centres performing thrombolysis for acute ischaemic stroke in EU countries, Norway and Iceland. Patients from these centres treated within the terms of the conditional product licence for alteplase were registered in SITS-MOST. The SITS-MOST protocol required the availability of an acute stroke unit with adequate monitoring, early mobilisation and rehabilitation facilities; and availability of a clinician trained in provision of thrombolytic therapy to monitor progress.

The SITS-ISTR is an internet-based interactive registry of stroke patients treated with thrombolysis which includes reports from the clinical stroke centres which did not participate in SITS-MOST, and also includes data from patients who did not meet the inclusion and exclusion criteria of the licence and who were therefore not included in the SITS-MOST study. SITS-ISTR participation simply required a commitment to register all patients treated with thrombolysis, to provide source data for monitoring and to provide clarification of potential adverse events when requested. There was no requirement to attend training in order to contribute to the SITS-ISTR. UK stroke physicians were required by conditions of the European Medicines Evaluation Agency (EMEA) licence and by their professional body, the British Association of Stroke Physicians (BASP), to register patients in SITS unless these patients were treated within another approved clinical trial of thrombolysis.

The SITS-MOST study protocol was reviewed by a UK multicentre research ethics committee (MREC A for Scotland) concluding that the study should be conducted as an anonymised audit. Within the UK, clinicians from the participating centres attended one-day thrombolysis training sessions organised jointly by SITS and BASP, at which instruction on the thrombolysis evidence base, the SITS-MOST protocol, outcome scales and logistical service issues were provided, together with an opportunity to discuss local difficulties with provision of thrombolytic therapy. Following these training days, participants were able to contribute data to the monitoring study.

In the UK, monitoring against the source data was performed by an experienced clinical research associate from an academic department, independent of the sponsor. Complications from intracerebral haemorrhage were independently evaluated. To facilitate comparison with other reported series, two commonly used criteria were employed. According to European Cooperative Acute Stroke Study (ECASS) Group criteria, a haemorrhagic complication was
defined as any ICH combined with a neurological deterioration of more than 4 points on the National Institutes of Health Stroke Scale (NIHSS) score from baseline, or from the lowest NIHSS value or death due to ICH within 7 days. According to the SITS-MOST criteria, a haemorrhagic complication was defined as local or remote parenchymal haemorrhage type 2 (defined as dense haematoma >30% of the infarcted area with substantial space-occupying effect or as any haemorrhagic lesion outside the infarcted area) on the 22–36 h post-treatment CT scan combined with neurological deterioration of 4 or more NIHSS points from baseline, or from the lowest NIHSS value between baseline and 24 h, or leading to death because of the intracerebral haemorrhage.

‘Experienced’ centres were defined as centres, which had participated in either of the European cooperative studies of thrombolysis or treated at least 5 patients before joining SITS-MOST. High volume centres were defined as those who registered more than 20 patients into the SITS registry.

Statistical testing
Descriptive statistics for baseline and demographic data were presented according to UK compared to other SITS-MOST patients excluding UK patients. Multivariate analyses were performed to examine if there was any difference in outcomes between UK SITS-MOST compared to the non-UK SITS-MOST patients excluding UK after adjusting for age, gender, hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, congestive heart failure, previous stroke, dependence before current stroke (defined as modified Rankin score 0–1), smoking, aspirin treatment at stroke onset, signs of current infarction in the baseline imaging study, patients treated in centres with previous thrombolysis experience, baseline NIHSS, blood pressure and blood glucose and stroke onset to treatment time.

Analyses presented were performed using MINITAB software (version 14, Minitab Inc. PA, USA). Multivariate analysis was performed by generalized linear or non-linear model using the STATISTICA (version 7.1, Statsoft Inc., OK, USA).

Results
Demography and logistics
A total of 614 patients treated in the UK were included in the SITS-MOST and SITS-ISTR registers over the period May 2002 to October 2006. Of the total 6483 patients and 285 centres in SITS-MOST, 327 patients (5.0%) were treated in 23 UK centres (8.1% of all the centres). The UK contributed 287 patients from 27 centres to the SITS-ISTR database. A total of 31 UK centres participated in the registers. The age, NIHSS and delay to treatment (onset-to-treatment-time, OTTT) for UK patients in SITS-MOST and SITS-ISTR with corresponding data for the non-UK SITS-MOST cohort are given in Table 1. A higher proportion of patients in the non-UK SITS-MOST registry had premorbid mRS scores of 0-1, indicative of minimal or no disability (93.3% vs. 90.2%, P=0.023). NIHSS score on admission was higher in the UK cohort compared to the non-UK cohort, and median OTTT was greater.

Provision of thrombolytic therapy was not uniform across the UK and the wide variation was unrelated to the population density (Figure 1). Centre activity (1–135) and assignment between SITS-MOST and SITS-ISTR both varied widely. Four centres did not attend the SITS-MOST training during the observation period thus all patients from these centres could be added only to SITS-ISTR. As all patients >80 years of age were automatically entered into SITS-ISTR and not SITS-MOST, the cohort of UK patients treated outwith SITS-MOST had a higher proportion of very old [66 (23%) SITS-ISTR patients were >80 years of age] patients. Overall, UK SITS-ISTR

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients in UK SITS-MOST, UK SITS-ISTR and non-UK SITS-MOST registries</th>
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<tbody>
<tr>
<td>UK SITS-MOST ( (n=327) )</td>
<td>UK SITS-ISTR ( (n=287) )</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>68 years (59–75)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>196 (60)</td>
</tr>
<tr>
<td>Median NIHSS (IQR)</td>
<td>14.5 (9–19)</td>
</tr>
<tr>
<td>Median OTT time (IQR)</td>
<td>155 min (130–170)</td>
</tr>
<tr>
<td>Median SBP (IQR)</td>
<td>148.5 mmHg (134–164)</td>
</tr>
<tr>
<td>Premorbid mRS (0–1), n (%)</td>
<td>294 (90.1)</td>
</tr>
<tr>
<td>Median glucose (IQR)</td>
<td>6.2 mmol/l (5.5–7.3)</td>
</tr>
<tr>
<td>Infarction on CT, n (%)</td>
<td>113 (35)</td>
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</table>
patients were older than UK SITS-MOST patients [mean (SD) age 69.3 years (14.0) vs. 65.7 years (11.6) \(P = 0.001\)], however no difference in stroke severity was apparent between these groups (median NIHSS 15 vs. 15, \(P = 0.52\)).

Ninety-one of 611 patients with known OTTT (14.9%) were thrombolysed after 3 h, of whom three were included in the SITS-MOST database due to intention to treat within licence. There was also a clear diurnal variation, with most activity occurring in the afternoon and evening. Only 24 of 614 patients (3.9%) were treated between midnight and 08.00 hours and only 16 of the 31 centres thrombolysed any patients between 9.00 p.m. and 8.00 a.m. A lower rate of thrombolysis was also apparent during weekends, when 113 patients (18.4%) were treated. The median delay from admission to brain imaging during working hours was \(\sim 1\) h for the total population.

Outcome was assessed at clinic review by the local clinical team using the modified Rankin scale (mRS) 3 months after treatment (Figure 4). Formal training in mRS scoring was available to centres\(^4\) but certification was not a requirement for participation.

In the UK, 29 patients (4.8%, 95% CI 3.4–6.8%) met the ECASS criteria for symptomatic intracerebral haemorrhage: 19 (5.99%, 95% CI 3.8–9.0%) of the SITS-MOST patients and 10 (3.6%, 95% CI 2.0–6.5%) of the SITS-ISTR patients. The corresponding ICH rate in the entire SITS-MOST cohort was 4.7% (95% CI 4.0–5.1, \(P = 0.31\) for UK SITS-MOST population vs. non-UK SITS-MOST cohort).

Ten patients met the SITS-MOST criteria for symptomatic intracerebral haemorrhage in the
UK: 8 (2.5%, 95% CI 1.3–4.8%) of the SITS-MOST patients and 2 (0.7%, 95% CI 0.2–2.5%) of the SITS-ISTR patients. The corresponding ICH rate in the non-UK SITS-MOST cohort was 1.7% (95% CI 1.4–2.0%, \( P = 0.28 \) for the comparison of UK SITS-MOST vs. the non-UK SITS-MOST cohort).

A smaller proportion of UK patients were treated in ‘experienced’ centres the UK compared to the non-UK SITS cohort (57% vs. 78%). In the UK there was no significant difference in mortality following treatment in an ‘experienced’ centre in comparison with a new centre (14.4% vs. 18.7%, \( P = 0.32 \)). Similarly, no difference in outcome was seen in ‘high-throughput’ centres compared to outcomes in ‘low-throughput’ centres (Figure 5).

In the multivariate analysis there was no statistically significant difference in any outcome between UK SITS-MOST compared to non-UK SITS-MOST excluding UK (\( P = 0.39 \) for SICH per SITS-MOST definition, \( P = 0.96 \) for SICH per RCT/Cochrane definition, \( P = 0.11 \) for mortality at 3 months and \( P = 0.35 \) for functional independence at months).

**Discussion**

The UK contains \( \sim 15\% \) of the pooled populations of the countries participating in SITS-MOST but contributed only 5% of cases to the SITS-MOST registry. Therefore a smaller proportion of patients are thrombolysed within the terms of the product licence in the UK as compared with other European countries. Relatively few stroke centres were active in provision of thrombolysis and there was significant geographic variability in UK registration irrespective of population density. This echoes the recent English national stroke audit,\(^4\) which identified substantial deficiencies in availability and quality of acute stroke care in the UK. That audit reported that 218 patients were thrombolysed in England, Wales and Northern Ireland in 1 year, suggesting that hospitals exaggerated their true figures, treated within clinical trials or failed to comply fully with professional and EMEA guidance in reporting to SITS; even the higher figure represents under 0.2% of acute stroke patients. Stroke services in Wales were especially weak, a finding underlined by the lack of any participating centre from that country in the SITS registry. Further reorganisation of stroke services is required to address this inequity of access to thrombolytic treatment for stroke in the UK.

The main rate-limiting step in provision of thrombolytic therapy is the three-hour time window. The ASSIST study\(^17\) showed that within the UK, 37% of stroke patients were already present in hospital within 3 h of onset of stroke. This suggests that changes to patient pathways within as well as outwith hospital are required before thrombolytic therapy for stroke will be more widely applied. For example, the median time from stroke to first brain imaging is 27 h in the UK, and only 15% of patients are admitted to a specialist stroke unit on the same day as their stroke occurs.\(^4\) In areas where the emergency services treat stroke with the same priority as acute myocardial infarction and are often the initial point of patient contact, admission to hospital is more rapid.\(^18\) A European study\(^19\) found that extensive reorganisation of ‘out-of-hospital’ stroke services on use of rt-PA substantially improved the proportion of patients thrombolysed.

The successful introduction of a streamlined referral triage protocol in Newcastle\(^20\) suggests that once suitable centres of expertise have become established in the UK, relatively simple measures will increase numbers of potentially treatable patients rapidly brought to appropriate facilities. However, there remains the potential for transport of patients ineligible for thrombolytic treatment to
centres that may be remote from their local hospital, without sufficient resources for comprehensive stroke care, as well as increasing the use of scarce ambulance resources. Major changes to the acute care pathway in stroke need to be part of an integrated whole system approach, with careful implementation of local guidelines and monitoring of service utilization.

Although outcomes in those UK centres with limited experience of rt-PA use were comparable to busier centres, (an observation previously reported in other phase 4 studies), provision of out-of-hours treatment in smaller centres represents a particular challenge, with only about half of all participating centres able to maintain such a service. Experience elsewhere suggests that teleradiology may have a role in improving access to thrombolysis in centres with access to out-of-hours computed tomography but with limited on-site expertise. UK experience with telemedicine and teleradiology is scant but the data presented suggest an unmet need for further exploration of initiatives which may improve access to thrombolytic therapy.

The median age of UK SITS-MOST participants matched that of the non-UK SITS-MOST cohort. Patients in the UK SITS-ISTR were older, however reflecting the absence of an upper age limit for registration. The median baseline NIHSS score in the UK SITS-MOST register was higher than for the non-UK SITS-MOST data (14.5 vs. 12), demonstrating that patients treated in the UK were more severely affected at baseline than their counterparts. This difference in severity is likely to be associated with a 15–20% absolute increase in the proportion of patients with poor outcome and could readily account for the outcome difference between UK SITS and non-UK SITS-MOST data. Our multivariate modelling supports this hypothesis. Further, there was a longer OTTT in the UK compared with the whole SITS-MOST register. These trends were also apparent prior to the inception of the SITS project, and a number of factors may be contributory. Selective recognition and transport of more severe stroke patients in the UK may play a role; however, an ongoing reluctance to treat mildly affected patients with an agent that also carries potential for harm may also have contributed. Our data from the SITS register suggest that these issues have yet to be addressed in the UK.

The outcome results for the patients in the UK SITS-MOST cohort were comparable to non-UK SITS-MOST data following correction for baseline disparities. It is worth noting that both the mortality and rate of symptomatic ICH observed amongst thrombolysed stroke patients in the UK remain consistent with those seen in the randomised trials of thrombolysis for stroke. Less clear is the underlying cause of the disparity in symptomatic ICH rate between UK SITS-MOST and SITS-ISTR cases. This observation differs from a previous study which suggested that protocol violations are strongly associated with haemorrhagic complications. Higher NIHSS scores and delayed treatment may predispose to increased symptomatic haemorrhagic transformation; however the numbers of patients with ICH according to either definition of symptomatic ICH are small, precluding definitive inferences. There were 11% more deaths in the SITS-ISTR-UK than in the SITS-MOST-UK cohort ($P=0.002$). It is possible that some patients died from an intracranial haemorrhage without undergoing a second CT scan, hence some of death rate excess in SITS-ISTR-UK could be explained by an excess of intracranial haemorrhagic complications. Such a hypothesis could explain the discrepancy in haemorrhage rates between SITS-ISTR and SITS-MOST in UK.

In conclusion, thrombolytic treatment in the UK has been implemented successfully but only in a relatively small number of centres and significant inequity of access exists across the country. Outcome data and complication rates are consistent with clinical trial experience but unfavourable differences in baseline patient characteristics and OTTT between the UK and the other participating countries are apparent. Although it is encouraging that access to thrombolysis in some areas of the UK matches that of major European and North American centres, it is clear that the challenge of equitable provision throughout the country has yet to be met.

**Acknowledgements**

We thank all the SITS investigators and their centres in the UK for their participation. The SITS-MOST register was funded by an unrestricted grant from Boehringer-Ingelheim GmbH (Ingelheim, Germany). Uppsala Clinical Research (Uppsala, Sweden) develops, maintains and upgrades the software for the SITS register. The study protocol for the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was drafted by SITS, Boehringer-Ingelheim and the European Medicines Evaluation Agency (EMEA). All data collection and analysis was performed independent of the sponsor. Biannual reports to the EMEA were written in parallel by SITS and Boehringer-Ingelheim independent of each other. In the UK, source data verification was performed by independent clinical...
staff under the direction of K.R.L. and G.A.F. Boehringer-Ingelheim was responsible for reporting of serious adverse drug reactions to regulatory authorities. Training meeting venues and speakers’ travel costs were paid by Boehringer-Ingelheim but no payments were made to speakers.

References


