The STRokE DOC trial technique: ‘video clip, drip, and/or ship’

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Rationale To describe the clinical trial methods of a site-independent telemedicine system used in stroke.
Aims A lack of readily available stroke expertise may partly explain the low rate of rt-PA use in acute stroke. Although telemedicine systems can reliably augment expertise available to rural settings, and may increase rt-PA use, point-to-point systems do require fixed base stations. Site-independent systems may minimize delay. The STRokE DOC trial assesses whether site-independent telemedicine effectively and efficiently brings rt-PA to a remote population.
Design STRokE DOC is a 5-year, 400-participant, noninvasive trial, comparing two consultative techniques at four remote sites. Participants are randomized to acute 'STRokE DOC telemedicine' or 'telephone' consultations. Treatment decision accuracy is adjudicated at two time points, using three levels of data availability and an independent auditor.
Study outcomes The primary outcome measure is whether there was a ‘correct decision to treat or not to treat using rt-PA’ at each of three adjudication levels (primarily at Level #2). Secondary outcomes include the number of thrombolytic recommendations, intracerebral hemorrhage, and 90-day outcomes. Using the STRokE DOC system (or telephone evaluation), medical history, neurologic scales, CT interpretations, and recommendations have been completed on over 200 participants to date. Of the initial 11, nonrandomized, ‘run-in’ patients, six (65%) were evaluated wirelessly, and five (45%) were evaluated with a site-independent LAN or cable modem. Three (27%) received rt-PA. The adjudication methodology was able to show both agreements and disagreements in these 11 cases. It is feasible to perform site-independent stroke consultations, and adjudicate those cases, using the STRokE DOC system and trial design. Telemedicine efficacy remains to be proven.

Key words: stroke, telemedicine, methods

Introduction

Although thrombolytic administration improves stroke outcome (1), 10 years after FDA approval thrombolytic therapy is administered to only 1–5% of stroke victims (2). A lack of readily available stroke expertise may partly explain the low treatment rate. Although published guidelines have been established (3), one-third of stroke patients are excluded from thrombolytic therapy because of rapid improvement or mild symptoms, were either dead, or dependent at hospital discharge (4). Thrombolytic therapy for acute stroke may result in hemorrhagic transformation, even if the protocol is followed scrupulously (5). To both assure that all eligible patients are treated and to reduce the hemorrhage rates, there is a need for both acute stroke expertise and rapid evaluation in more emergency departments (ED).

One-third of the US population lives in a rural area (6). Underserved areas rarely have dedicated stroke teams, or are located too far away for practitioners with such expertise to treat rapidly with thrombolytics. Many leading stroke centers maintain active Code Stroke teams that evaluate patients at nearby EDs, while telemedicine systems may improve rural access to medical expertise (7).

The issue of telemedicine’s reliability has been addressed (8–10). One study using fixed communication lines showed an excellent interrater reliability in 40% of the NIHSS items and a total NIHSS score intraclass correlation coefficient of 0.97 (8). Reliability was shown using a web-based design for video, and standard telephone connection for audio, with excellent...
agreement between the bedside and remote locations \((r = 0.9552)\) (9). The STRoK E DOC system, using a site-independent, two-way audio and video, Internet-based system showed excellent reliability in 67% of the NIHSS items and 82% of the mNIHSS items (10).

Levine and Gorman noted the potential benefits and limitations of telemedicine specifically for stroke (11), although already this technology is being used on a daily basis for stroke care and rt-PA (12, 13). There are numerous systems in use ranging from ‘off-the-shelf’ point-to-point teleconferencing software to highly complex, site-independent, web-based access or Internet-based systems. Technical requirements and clinical protocols have not been standardized.

Implicit in the expanded use of telemedicine is an assumption that it safely, effectively, and efficiently brings rt-PA to a population that may otherwise go without. The assessment of telemedicine’s efficacy in stroke should include both increasing the numbers of rt-PA treatments and also assessing the proportion of correct decisions to treat or not to treat when utilizing such a system. The purpose of this clinical trial is to assess these assumptions, comparing a site-independent telemedicine system with telephone consultation.

**Methods**

**Design**

This is a 5-year, randomized, noninvasive, 400-participant clinical trial assessing two consultative techniques for use in acute stroke. Patients are randomized to either ‘Telemedicine’ or ‘Telephone-Only’ consultations using permuted blocks of two or four, stratified by study site. This guarantees balance within each site and prevents imbalance at any time in the study. The trial was approved by the UCSD Human Research Protections Program.

The equipment for this study includes an Internet-enabled laptop computer, a high data rate (HDR) modem, and the STRoK E DOC audio/video teleconsultation system. The wireless, CDMA 2000 1× EV-DO Qualcomm \(^\text{TM}\) modem (Qualcomm \(^\text{TM}\) Inc., San Diego, CA, USA) allows high bandwidth wireless Internet access. The AccessVideo \(^\text{TM}\) software (BF Technologies Inc.) enables site-independent hub consultant access to audio, video, and radiographic data (Figs 1 and 2) irrespective of wireless or wired access. This video over Internet system uses novel Quality of Service error correction technology, Microsoft Windows Media 9 video compression, 400 × 300 resolution (maximum 640 × 480), full 30 frames/second video, and fully synchronized audio to enable multimedia patient evaluations using currently available Internet (> 300 kbps) technology.

The high-resolution camera at the remote hospital (spoke) is a Sony EVI-D70 camera (Sony \(^\text{TM}\) Inc., Tokyo, Japan) with remote pan, tilt, and zoom capabilities. For remote access, a Pentium \(^\text{TM}\) IV, 2000 MHz mobile laptop computer with 1024 Mb of RAM, 14’ XGA TFT LCD display at 1024 × 768 resolution, built-in wireless 802 11b, and Ethernet capability was used.

**Patient population**

In the first phase of this experiment, telemedicine reliability, and validity assessments were performed for patients with stable clinical deficits. Those results have been published previously (10). Eleven nonrandomized ‘run-in’ acute stroke consults were then performed in an initial experience. Consultations are currently being performed at up to four remote sites (Pioneers Memorial Hospital, El Centro Regional Medical Center, Palomar Memorial Hospital, and Twin Cities Community Hospital). These four full-service hospital EDs are regional community medical centers with 50–200 beds, and range in distance from 30 to 350 miles from UCSD. Remote facilities (spokes) are accessed using the software from site-independent locations (by the hub consultant).

**Randomization**

Patients are included in the acute consultation portion of the trial if they are ≥18 years of age, have symptoms consistent with acute stroke (ischemic or hemorrhagic), have initial onset generally felt to be < 12 h and likely < 3 h, and where written informed consent can be obtained from the patient (or healthcare surrogate if indicated). They are excluded if they are felt to be unlikely to complete the study through the 90-day follow-up.

For acute stroke consultations, an Emergency Medicine practitioner at one of the remote spoke sites contacts the UCSD Stroke Team by a standardized pager system. The UCSD consultant immediately contacts the spoke facility via telephone. Patients or designated healthcare surrogates are required to sign consent forms for enrollment. In keeping with the site-independent technique, these consent forms are faxed and accessed by the UCSD consultant using an Internet fax technique. The consultant randomizes the participant to receive either a prospective ‘Telemedicine’ or ‘Telephone-Only’ consultation using a web-based randomization system, thus eliminating practitioner preference bias. Once randomized, the consultant performs the consult using that designated modality.

If the patient is randomized to the telemedicine modality, the consult commences using the STRoK E DOC telemedicine system. The consultant site independently accesses the camera system. The single requirement of the spoke practitioner is to ensure that the mobile camera server (IV pole design) is placed at the foot of the patient’s bed. All control of the system is left to the telemedicine practitioner. Via this system, the patient’s relevant head CT scan images are also remotely viewed during the consultation. If the patient is randomized to the telephone-only modality, the consult commences using only the telephone. The consultant does not utilize the camera system for video or radiology imaging. The spoke practitioner discusses the case
with the telemedicine practitioner via telephone, including reporting the local radiology interpretation of the CT scan.

A consultation includes performing a complete history, physical assessment, clinical deficit scales (including the NIHSS), head CT imaging evaluations, and providing diagnostic and therapeutic recommendations, including the use of rt-PA, to the requesting ED practitioner. The UCSD consultant records all study data on paper or web-based case report forms. Connection type is recorded and relevant time points are documented.

Treatment

Upon completion of the consultation, recommendation comments are dictated into the medical record. These comments may include recommendations regarding further lab or procedural testing, IV fluid choices, medications, or administering thrombolytic therapies. This trial did not preclude local neurology consults if they became available at any point. If patients receive thrombolytics, follow-up imaging for hemorrhage within 36 h is performed. Patients are contacted for functional assessments at 90 days by a study nurse via telephone.

Primary outcomes

The primary outcome measure in this trial is whether the decision to treat, or not to treat, with thrombolytics is appropriate. The decision to treat is adjudicated at two time points, using three levels of data availability (Table 1). Level I review is performed at a meeting of the STRoE DOC Adjudication Committee (SDAC) on the first available Thursday following the consultation. This level determines whether the treatment decision was ‘appropriate: given the information available to and presented to the remote consultant.’ This level assumes that there may be information not available to the consultant. In order to avoid unblinding, treatment arm is not reported, stroke scale scores are not reported, and case discussions include statements such as ‘as seen by me on video, or as reported to me via telephone.’ CT scan results are reported in a similar manner. The consulting practitioner, monitor, and any unblinded team member leave the room during voting. The SDAC determines whether the decision to treat or not treat was appropriate based on Level I information.

Level II review is the primary outcome review level and is performed on the first available Thursday following the Medical Monitor review. This allows the monitor to collect relevant data that would have been available had the consultant been physically present at the bedside at the time of the consult. This level determines whether the treatment decision was ‘appropriate: based on all information available at the ED bedside, even if not presented to or found by the remote consultant.’ This level assumes that there may be information that was not available to the consultant at the time of evaluation that would have been available if physically located at the bedside during the consult. The monitor’s adjudication at Level II is based on standard inclusion/exclusion criteria in the protocol. The SDAC reviews the monitor’s data and decision, discusses the case, and makes a separate Level II determination, without the consultant or monitor in the room during discussion and voting. At Level II, the SDAC refers to

Fig. 1 AccessVideo™ Video Images. Patient with right MCA cerebral infarction (images show pan/tilt/zoom capability). (top left) Left facial droop. Right gaze preference not shown. (top right) Real-time vital sign monitoring. (bottom left) Left arm drift. (bottom right) Left arm with good strength when stimulus addressed to left (grandchild).
clinical guidelines and community standard where indicated, and defaults to practitioner experience in qualitative discrepancies not explicitly addressed in thrombolytic guidelines (e.g. degree of blood pressure treatment, patient age, CT findings).

Level III is a retrospective review of the case. At Level III, the medical monitor will assess data (irrespective of availability to the consulting practitioner) from the acute hospitalization. This level determines whether the treatment decision was ‘appropriate: based on retrospective review of all data, at time of decision, whether available, known or unknown at that time.’ This review is not based on patient outcome, but on data that are subsequently found, which could have been known at the time of decision (e.g. subsequent MRI showing brain tumor, not stroke). Similar to Level II, the medical monitor renders a vote, as does the SDAC, but leaves the room during the committee discussion and voting.

The CT scan assessment is also adjudicated. During the initial consult, the acute head CT scans are interpreted. If the patient is randomized to telemedicine, the baseline head CT scan is visualized, preferably using the STRokE DOC system’s DICOM server and radiology access system. If the patient is randomized to telephone, the baseline head CT scan is not visualized, and the standard local radiology read is used as the baseline read. All images are collected, de-identified, and assigned a unique DICOM identifier, unrelated to the SPOT-RIAS patient identifier, in order to avoid bias.

All CT scans will be centrally read by blinded readers, the STRokE DOC–Radiology Central Review Committee (STRokE DOC–RCRC), in order to: (1) assess the reliability of telemedicine for acute stroke head CT interpretation and (2) assess the ability of a stroke neurologist to act as a surrogate for a radiologist in the acute interpretation of stroke head CT scans. Central reads will be compared with teleradiology interpretations (n = ~200) and local radiology interpretations (n = ~200). Individual items including evidence and location of stroke, edema, hemorrhage, tumor, or hyperdense artery sign will be scored. Standard, clear radiographic contraindications to rt-PA are referenced [e.g. intracerebral hemorrhages (ICH) on baseline CT scan]. Regarding issues that are less agreed upon, the STRokE DOC–RCRC makes a single, consensus vote on the question ‘Is there a CT contraindication to thrombolytic therapy?’ The radiologist’s vote is weighted to account for radiographic image interpretation experience.

**Secondary outcomes**

Although the primary outcome of assessing the correctness of treatment decision is important, there are other equally integral comparisons that will be assessed. These include determining the absolute number of thrombolytic therapy administrations in each arm, assessing functional outcome measures (modified Rankin Scale) at 90 days, comparing the number of ICH and systemic bleeding complications, and recording any technical observations related to either the telemedicine or telephone consultation technique.

**Data monitoring body**

An independent medical monitor performs case-related data collections for the adjudication process as noted above, and
monitors the data recorded in the SPOTRIAS database/case report forms. A clinical steering committee has been convened to oversee issues related to the clinical trial itself.

**Sample size**

Sample size ($n = 400$) calculations were based on a $\chi^2$ square test to detect a difference between two proportions (two-sided $\alpha = 0.05$). Assuming a correct telephone decision rate of 80%, a sample size of 200 patients per arm has an 80% power to detect a correct decision rate of 90% in the telemedicine group. Primary analysis will be a random-effects logistic regression model (clusters will be the study sites) to test the effect of the consultation group on the correct decision for thrombolytic treatment.

**Statistical analyses**

Results from 11 initial acute stroke consultations are included only to show feasibility and to address the adjudication design. There were no technical failures, with all 11/11 (100%) evaluations being performed using the STRoke DOC system. Three of the 11 patients received rt-PA. Adjudication was performed on all 11/11 patients, and 90-day assessments were completed on 10/11 patients (one lost to follow-up). Adjudication results showed 100% agreement at Level I. Of the rt-PA-excluded patients, there were no Level II or III discrepancies between the monitor’s interpretation and that of the SDAC. Of the rt-PA-treated patients, in one case the SDAC disagreed with the treatment decision only at Level III (because information became available only retrospectively that the symptoms may have been present for $>3$ h). In another case, the medical monitor noted a contraindication (a GI bleed occurring 18 days before treatment) but the SDAC review concurred with the original decision to treat, as the prior GI bleed was definitively treated.

To date, over 200 participants have been enrolled in the STRoke DOC trial, randomized to telemedicine or telephone consultation. Information regarding percentage in each arm receiving rt-PA, having complications, or obtaining favorable adjudications will not be available until the trial’s completion. Assessment of issues surrounding the technique of obtaining Informed Consent is also not yet available.

**Study organization and funding**

This work was supported by the National Institute of Neurological Disorders and Stroke (P50NS044148), the California Table 1 Adjudication log: (a) Data collection and (b) Adjudication results

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*Original SPOTRIAS ID, consultant, connection type, whether rt-PA was recommended and given, and exclusion reason. All ‘run-in’ patients received telemedicine (TM) consultations. †Original SPOTRIAS ID and STRoke DOC Adjudication Committee (SDAC) and monitor adjudications. Disagreements and related comments are shown. ICH, intracerebral hemorrhages.
was kept broad. This initial choice of trial design will indeed minimize the spoke practitioners’ burden of determining the precise time of onset become available. We strove to make it not to limit the inclusion to 3 h only as the time of onset may not be known, and only during the stroke evaluation does the treatment decision to treat or not to treat cannot be determined until the completion of this or other trials.

One potential solution could be to increase stroke patient transfers using ground or aeromedical transport (14, 15). However, time and distance preclude the transfer of all patients before rt-PA treatment. Administering rt-PA and transferring patients, the standard ‘Drip & Ship’ approach, may result in retrospective concern over whether the patient should have been treated, given limited expertise available at the time of the treatment. This ‘Drip & Ship’ approach (16) may be augmented by either telephone (17) or by one of many available telemedicine systems (10, 12, 13, 18, 19).

Our previous assessments have ensured a reliable site-independent telemedicine consultation system (10). Any such system should be tested for reliability, or should conform to the requirements of this or other reliability studies, before commencing with acute stroke consultations. Telemedicine can be used to increase the numbers of rt-PA administrations. The question of whether this increase correlates with a correct decision to treat or not to treat cannot be determined until the completion of this or other trials.

The adjudication methodology (Table 1) is able to document issues related to efficacy: instances of appropriate rt-PA treatments, appropriate non-treatments, protocol violations, and retrospective disagreements regarding treatment decisions. The novel methodology may help determine whether telemedicine will result in more appropriate rt-PA treatment decisions.

One limitation of this trial may relate to the initial ‘time of onset’ inclusion criteria. Investigators felt that it was imperative not to limit the inclusion to 3 h only as the time of onset may not be known, and only during the stroke evaluation does the precise time of onset become available. We strove to maximize the evaluation of all rt-PA eligible patients, and minimize the spoke practitioners’ burden of determining the final time of onset before initiating the consult. A secondary outcome of this trial assesses patient outcome irrespective of rt-PA recommendation. For these reasons, the time inclusion was kept broad. This initial choice of trial design will indeed result in an artificially increased percent of agreement that rt-PA was not indicated in late-arriving patients, as we are generally following standard NINDS rt-PA protocol recommendations for treatment within 3 h.

Although increased numbers of rt-PA, and appropriate decision to treat and not to treat, will be assessed for in this trial, some questions will remain even upon the trial’s completion. Issues of liability are not fully determined, although mandating a face-to-face (two-way audio and video) telemedicine consultation will likely make liability similar to that of standard consultations. Although not assessed in this trial, the one-time cost of installing a site-independent telemedicine system likely outweighs the recurrent costs of transporting patients via life flight. Telemedicine may satisfy the Brain Attack Coalition’s recommendations for continuous stroke practitioner availability (2), and may be appropriate for use in satisfying the Joint Commission on the Accreditation of Hospital Organizations requirements for Primary Stroke Center certification.

Telemedicine consultations have increased two- to threefold annually since 1994 (11). Given its significant availability, it is now quite clear that the era of stroke telemedicine is upon us, and the adage of ‘Drip & Ship’ might soon be replaced by that of ‘Video Clip, Drip and/or Ship.’

References


Institute of Telecommunications Technology, and by the Veterans’ Affairs Department, Research Division. Brett C. Meyer is the Principal Investigator for the STRoK E DOC trial. Rema Raman, Ramesh Rao, Janet Werner, Justin Zivin, and Patrick Lyden are collaborators and key personnel for the trial. Ronald Fellman and John Beer are founders of BF Technologies Inc. (AccessVideo™ Telemedicine system).

To maximize benefit and minimize risk, stroke-trained practitioners with expertise in evaluating neurologic deficits, interpreting CT scan images, and assessing for exclusion criteria are needed. Until recently, treatment has been limited to geographic regions having stroke expertise. To provide stroke expertise, practitioners may drive to nearby facilities or acute patients may be brought to the tertiary care facility emergently. Neither of these systems is easily sustainable nor easily implemented nationwide. Techniques aimed at increasing rt-PA treatments have thus far not resulted in robust successes (2).