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Enrollment of Research Subjects through Telemedicine Networks in a Multicenter Acute Intracerebral Hemorrhage Clinical Trial: Design and Methods

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Abstract

Background: Enrollment of subjects in acute stroke trials is often hindered by narrow timeframes, because a large proportion of patients arrive via transfers from outside facilities rather than primary arrival at the enrolling hospital.

Rationale: Telemedicine networks have been increasingly utilized for provision of care for acute stroke patients at facilities outside of major academic centers. Treatment decisions made through Telemedicine networks in patients with acute ischemic stroke have been shown to be safe, reliable, and effective. With the expanding use of this technology and the impediments to enrolling subjects into clinical trials, this approach can be applied successfully to the field of clinical research.

Methods and Conclusions: The antihypertensive treatment of acute cerebral hemorrhage II trial is a phase III randomized multicenter trial that has developed a protocol in collaboration with participating sites to implement the use of Telemedicine networks for the enrollment of research subjects. The protocol describes the operating procedures and legal and Institutional Review Board perspectives for its implementation.

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Journal of Vascular and Interventional Neurology
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Introduction

Spontaneous intracerebral hemorrhage (ICH) has a worldwide incidence of 24.6/100,000 person-years with approximately 40,000–67,000 cases/year occurring in the United States[1-3]. Despite the high mortality and disability rate associated with ICH[3], there is lack of an effective treatment that results in reducing mortality and disability.

There are currently at least 33 ongoing clinical trials and observational studies enrolling patients with ICH. Taking into account the time window for enrollment, 15 (45%) of these trials are recruiting within 4.5–24 hrs after the onset of symptoms (ClinicalTrials.gov). The difficulties that these time-sensitive trials impose to enroll subjects have been noted[4]. One of the main reasons for exclusion is the fact that potentially eligible subjects do not arrive within the time window for enrollment, mainly because patients' arrival to the hospital is delayed. Additionally, many potentially eligible patients present to non-enrolling medical institutions initially and then are subsequently transferred to the hospital where the study is being conducted. Current estimates from national and regional data suggest that approximately one-fifth of patients with acute ischemic stroke arrive as transfers from outside facilities in the acute setting[5,6]. For ICH cases a recent single-center prospective study reported a 42% rate of transfer among their ICH cases[7].

The antihypertensive treatment of acute cerebral hemorrhage (ATACH) II trial is an ongoing phase III randomized multi-center clinical trial of blood pressure (BP) reduction for acute hypertensive response in ICH (ClinicalTrials.gov [NCT01176565]). The description of its methodology and design was previously published[8]. Inclusion and exclusion criteria are outlined in Table 1. Briefly, the ATACH II trial is a parallel, two-arm study, in which the eligible subjects with supratentorial ICH are randomized in an 1:1 ratio to intense systolic blood pressure (SBP) reduction (SBP $\leq$ 140 mmHg) or standard SBP reduction (SBP $\leq$ 180 mmHg) within 4.5 hrs of symptom onset. The treatment protocol involves the infusion of intravenous (IV) nicardipine for 24-hr post-randomization. The primary study objective is to determine the therapeutic benefit of intensive SBP treatment compared with standard SBP treatment in reducing the proportion of patients with death or significant disability (modified Rankin scale, mRS of 4–6) at Day 90.

In this article, we describe the methodology for the utilization of telemedicine in the screening and enrollment of subjects in the ATACH II trial.

Objective

We address the challenge of patient recruitment in a short time window in the ATACH-II trial through the incorporation of telemedicine-based screening and enrollment. We expect that this effort will act as a template for this novel technological approach in current and future trials in patients with acute stroke.

Background and Rationale

Telemedicine is defined as "the use of telecommunication technologies to provide medical information and services"[9]. It is utilized in different medical specialties and its name is usually adapted to reflect those disease-specific Telemedicine networks. "Telestroke" has been defined as the application of telemedicine in stroke care[10] and it is characterized by the remote evaluation of a patient with stroke symptoms by telephone consultation or video-teleconferencing (VTC) and the transfer of imaging data [computed tomography (CT) or magnetic resonance imaging (MRI)] for interpretation and decision making[11].

A typical Telestroke network can be organized using the hub and spoke model,[12] in which the "spoke" hospital is usually a community center sometimes located in rural areas without 24/7 coverage by vascular neurologists or other stroke expertise. In this model, the "hub" hospital is usually a tertiary care facility, commonly a primary or comprehensive stroke center located in urban areas with 24 hrs availability of trained stroke specialists. Under this model, those patients that present at a spoke hospital are evaluated by the healthcare personnel who then activate the Telestroke network through a video-based connection with the hub hospital. At the hub hospital, the vascular neurologist reviews the history and performs a video-based physical examination and evaluates available neuroimages that are transferred to a dedicated image server. An alternative to this approach is to share the screen with the hub site to expedite the imaging evaluation. After evaluation, decisions regarding disposition and medical care are made, often resulting in the transfer of patients to the hub site (where more advanced therapy or inclusion in clinical trials can be offered), or continuity of care at the spoke center.

A recent review from a scientific committee from the American Heart Association (AHA) / American Stroke Association (ASA) regarding the use of Telemedicine in stroke systems concluded, among other things, that: (1) the National Institutes of Health Stroke Scale (NIHSS)

Journal of Vascular and Interventional Neurology

Table 1.
ATACH-II criteria for enrollment.

Inclusion Criteria:

- Age 18 years or older.
- IV nicardipine can be initiated within 4.5 hrs of symptom onset.
- Clinical signs consistent with the diagnosis of stroke, including impairment of language, motor function, cognition, and/or gaze, vision, or neglect.
- Total GCS score (aggregate of verbal, eye, and motor response scores) of 5 or greater at time of ED arrival.
- INR value < 1.5.
- CT scan demonstrates intraparenchymal hematoma with manual hematoma volume measurement <60 cc.
- For subjects randomized prior to IV antihypertensive administration: SBP > 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT spontaneous SBP reduction to below 180 mmHg at the time of randomization OR.
- For subjects randomized after IV antihypertensive administration: SBP > 180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment) AND WITHOUT SBP reduction to < 140 mmHg at the time of randomization.
- Informed consent obtained by subject, legally authorized representative (LAR), or next of kin.
  - Note: Patients with SBP < 180 mmHg should be monitored for 4.5 hrs from symptom onset as their SBP may rise to eligible levels before the eligibility window closes.

Exclusion Criteria:

- ICH is due to previously known neoplasms, AVM, or aneurysms.
- Intracerebral hematoma considered to be related to trauma.
- ICH located in infratentorial regions such as pons or cerebellum.
- IVH associated with intraparenchymal hemorrhage and blood completely fills one lateral ventricle or more than half of both ventricles.
- Patient to receive immediate surgical evacuation.
- Current pregnancy or parturition within previous 30 days, or active lactation.
- Use of dabigatran within the last 48 hrs.
- A platelet count < 50,000 mm^3
- Known sensitivity to nicardipine.
- Pre-morbid disability requiring assistance in ambulation or activities of daily living.
- Subject's living will precludes aggressive ICU management.
- Subject is currently participating in another interventional clinical trial.

examination by Telestroke is recommended when administered by a stroke specialist when such specialist is not immediately available in the acute setting; (2) the use of teleradiology is recommended for the evaluation of brain CT imaging and identification of exclusions for thrombolytic therapy in acute ischemic stroke; (3) it is recommended that the stroke specialist give their medical opinion in favor of or against the use of thrombolytics via telemedicine when on-site stroke expertise is not immediately available; (4) pre-hospital telephone communication between emergency medical services (EMS) personnel and stroke specialists can be effective in facilitating enrollment into hyperacute neuroprotective trials[13].

As discussed above, telestroke networks are primarily used in acute ischemic stroke to facilitate the use of thrombolytics and have proven to be safe and effective in the clinical setting[14, 15]. Telestroke is also used in cases of ICH and a recent publication analyzed an 8-year experience, during which 733 patients with ICH were evaluated and their treatment and transport disposition were decided using telestroke. Decision to transfer patients was based on hematoma location, size, and CT

Journal of Vascular and Interventional Neurology

Table 2.

The step-by-step procedure for enrollment via telestroke networks.

The following outline provides general guidelines that should be utilized by ATACH-II clinical sites relying on telemedicine for subject enrollment. Some site-specific adjustments are expected as each ATACH-II clinical site has a different telemedicine infrastructure in place. Before the implementation of this procedure, the ATACH-II clinical site must have its local Internal Review Board (IRB) approve the telemedicine procedure that will be implemented.

1. The hub site will identify spoke sites within a transfer time ceiling not > 2.5 hrs by either ground or air.
2. The hub site will identify Emergency Departments at spokes that have nicardipine stocked at their pharmacies. Nicardipine on-site will make subject randomization possible at a spoke center that will later transfer the subject while actively getting the study drug. At spoke centers that do not stock nicardipine, only screening and optimization of transfer could be performed. Normal study procedures will be resumed when patient arrives at the hub.
3. After a patient has been diagnosed with ICH by CT imaging at the spoke, clinicians need to contact the hub via telemedicine, and discuss treatment options along with the inclusion/exclusion criteria for the trial.
4. The CT will be reviewed by the investigator at the hub in real time; the ATACH-II investigator will determine the hematoma volume using the ABC/2 technique.
5. If enrollment criteria are met, clinicians at the hub should discuss the clinical trial and the informed consent form with the patient or the LAR to save time.
6. If patient or LAR agrees to participate in the trial, documentation of informed consent can occur by at least two different ways, depending on local IRB regulations.

   6a: The Informed Consent Form (ICF) will be faxed to the spoke site with the date, time, and signature of the investigator at the hub site. The subject or LAR will then sign the ICF and fax it to the hub site. Local IRBs may require a witness to validate the authenticity of the signature and may require the subject or LAR to re-consent in person upon arrival at the ATACH-II site.

   6b: The subject or LAR will sign a local paper copy of the consent form while at the spoke site after providing verbal consent to the investigator over telemedicine and will bring the form to the primary hub site. After arrival to the hub site, the ICF will be signed by the local investigator. Local IRBs may require a witness to validate the authenticity of the signature. The witness may be required to sign the informed consent form. Local IRBs may require the subject or LAR to re-consent in person upon arrival at the ATACH-II site.
7. After consent is obtained, randomization may be executed.
   - NOTE: transfer of patients will only occur if clinically necessary. Patients will not be transferred only for trial enrollment.
8. Nicardipine may have been initiated before randomization according to the trial protocol, but after randomization, it should be titrated to the BP goal determined by the randomization arm (<180 versus <140 mmHg).
9. Treatment goal and monitoring frequencies will be communicated to the EMS personnel.
10. Upon the patient's arrival at the hub site, continuous adherence to the protocol should be followed.
    - NOTE: according to the current manual of procedures, nicardipine can be initiated up to 30 min after randomization through telemedicine, as long as the drug initiation time remains < 4.5 hrs from symptoms onset.

features in combination with age, relevant clinical data and overall neurological status. The time needed for a neurosurgical consultation from initial admission at the hub hospital was significantly lower when using telestroke compared with the time before the introduction of the telemedicine system (38 min versus 160 min). Also, the use of telestroke made the decision of transferring the patient more efficient, effective, and rapid[16].

Telestroke technology was also implemented in a research setting and proved to be a very successful tool for enrollment of subjects in a clinical site that evaluated it in two acute stroke trials, one of them being a large multicenter trial in ICH, Factor Seven for Acute Hemorrhagic Stroke or FAST trial[17]. The second trial, Minocycline to Improve Neurological Outcome in Stroke or MINO trial was a study that evaluated IV minocycline in acute ischemic stroke[18]. In this study, the majority of the 28 subjects enrolled in both trials (19 or 68%) were initially identified via telestroke. The FAST trial had a time window of 3 hrs from symptom onset for the diagnosis with a CT scan, and up to 4 hrs for randomization. The

Journal of Vascular and Interventional Neurology

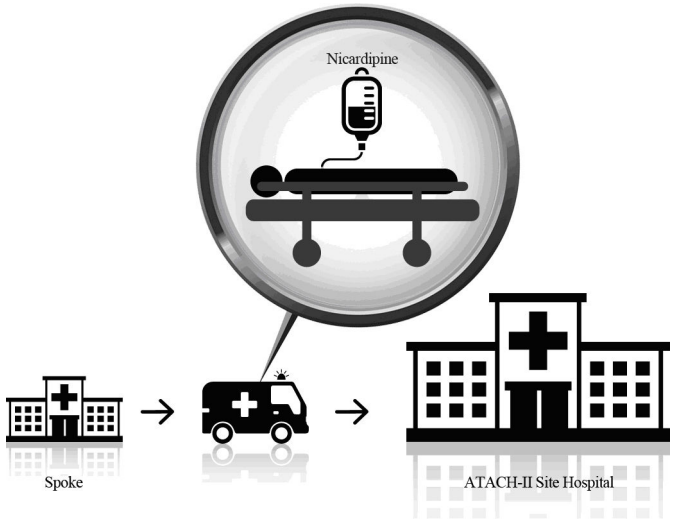

Figure 1. Schematic representation of a research subject being transported after randomization at a spoke hospital.

MINO trial had a window of 6 hrs for enrollment. Although telestroke was utilized to screen and identify potential candidates, informed consent forms were faxed to the spoke site on two occasions, signed locally by a Legally–Authorized Representative (LAR) then taken to the hub where they were signed by a study investigator. The median time from the arrival of patients at the hub ED to the initiation of study drug in both trials was significantly shorter in those subjects identified by telestroke at spoke hospitals and then transferred, versus those who presented directly to hub ED:71 min (95% CI 62-104) versus 140 min (95% CI 94-188), p = 0.002. This reduction in time to randomization was attributed to the fact that advanced notification and previous trial discussion help prevent delays in initiating study drug. The investigators concluded that telestroke increases enrollment in acute stroke trials and strongly encouraged the initiation of study drug while the patient is still at the remote spoke hospital,[19] which is the main goal for the involvement of telestroke in our trial.

Design and Methods

Currently 46 sites in the United States (U.S.) and 20 international sites are participating in ATACH II. From the U.S. sites, we have identified 18 telestroke networks among those clinical sites participating in the trial. These networks include those that are currently active and being used for clinical purposes and the ones that are being set-up and will be active in a short period of time. These telestroke networks cover more than 105 spoke centers. Sites were identified using data from a recently published article on the status of telestroke in the United States,[20] by an internal survey sent to all our U.S. sites and by voluntary contact from those sites with active networks that were not identified by the previous two methods, but who became aware of the proposal after internal communications through newsletters and teleconferences.

We developed a Standard Operating Procedures (SOP) manual for the screening and enrollment of patients in our study using telemedicine technology (Table 2). In our model, the hub hospital is a clinical center currently participating in the ATACH-II trial, while the spoke hospital is a center that is part of an existing local telestroke network as defined previously[12]. The final overall goal is to screen, obtain consent, randomize, and initiate study drug while the patient is still at the spoke hospital in an approach that we call “randomize, initiate, and ship.” General procedures start when patients arrive at the spoke site with stroke symptoms. Once these patients have been identified with a potential diagnosis of stroke, local standard diagnostic procedures should follow, including acquisition of a non-contrast CT scan of the brain. After the diagnosis of ICH has been made, the telestroke network will be activated to discuss therapeutic options and the ATACH-II inclusion/exclusion criteria with a study investigator located at the hub hospital. If a patient meets enrollment criteria for the study, enrollment in the trial will be discussed with the clinician, the patient and/or LAR, and if the subject or LAR provides consent, the study protocol will be followed, explained in more detail in Table 2.

By incorporating this clinical trial in an already established telestroke network, in which patients with ICH are transferred by EMS, we will communicate the

Journal of Vascular and Interventional Neurology

Journal of Vascular and Interventional Neurology

assigned treatment goal and BP monitoring frequencies to the EMS crew (Figure 1).

In anticipation of the incorporation of telestroke into ATACH-II, an update to our existing mobile application in 2012 was made to provide a pre-screening tool allowing the preliminary assessment of subjects and the identification of the nearest enrolling site using a global positioning system (GPS)[21]. The prescreening tool was developed for referring hospital staff, CT technologists, and nursing staff. This feature allows selecting a user type and having inclusion/exclusion criteria for each user type. Users have the ability to mark yes or no for each question, and if all questions are marked yes they will be brought to the site locator to find the nearest clinical trial center and contact information. This application is available on iPhones, Blackberries, and Android-based smart phones. The server is a standard HTTP server and the website does not require use of Adobe Flash or third party JavaScript components.

Conclusions

With the expansion of telestroke across the United States, there is a tremendous opportunity to leverage this resource for diagnosis, expedited treatment, transport and enrollment of subjects in the ATACH-II trial and clinical trials of ICH and acute stroke in general. We are actively pursuing telestroke enrollment and hope to demonstrate the feasibility, safety and benefits of its use in ICH trials. With this project we aim to enhance the basis for the systematic use of telestroke networks in clinical trials related to ICH and other forms of stroke.

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