Prehospital Reversal of Warfarin-Related Coagulopathy in Intracerebral Hemorrhage in a Mobile Stroke Treatment Unit

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Warfarin-related intracerebral hemorrhage (ICH) accounts for 15% to 20% of all intraparenchymal hemorrhages and is associated with a much higher mortality than spontaneous ICH. Although rapid (ie, within 2 hours of onset) reversal of warfarin effect has been advocated, significant delays in initiation of therapy and correction of international normalized ratio are common. 

Solution
A mobile stroke treatment unit (MSTU) can deliver prehospital stroke care and can shorten the time to thrombolytic therapy in patients with ischemic stroke. MSTU can also deliver other therapies in acute neurological emergencies.

Methods
Cleveland Clinic in collaboration with the Emergency Medical Services of the City of Cleveland implemented an MSTU starting July 18, 2014. We report on the prospectively collected data through August 31, 2014.

The on-board MSTU team consists of a registered nurse, paramedic, emergency medical technician, and a computed tomography (CT) technologist. A cerebrovascular specialist evaluates the patient via telemedicine (InTouch RP-Xpress, Santa Barbara, CA), whereas a neuroradiologist remotely evaluates images obtained by a portable CT scanner (CereTom, Neurologica Corporation, Danvers, MA). Point-of-care laboratory testing routinely performed includes coagulation profile (coaguChek XS Pro, Roche Diagnostics, Indianapolis, IN), complete blood count (pocH 100i hematology analyzer, Sysmex Corporation, Kobe, Japan), and blood chemistry (iSTAT System, Abbott Laboratories, Abbott Park, IL).

A City of Cleveland Emergency Medical Services (EMS) dispatcher identifies potential stroke and dispatches both a standard ambulance and the MSTU to the scene. After the city EMS squad screens for acute stroke, the MSTU team brings the patients to the MSTU and draws blood, places intravenous catheters, and obtains CT scan. After remote physician evaluation and CT interpretation, treatment decision is made.

Result of Initial Pilot Implementation
Three patients with ICH were among the 54 subjects evaluated by the MSTU during this period of time. One of them had a warfarin-induced coagulopathy. A 93-year-old woman on warfarin with history of cardioembolic strokes secondary to atrial fibrillation was found by family members in bed with right hemiparesis and decreased fluency, leading to activation of EMS services.

The MSTU was dispatched and the patient entered the unit 17 minutes after dispatch. Head CT was completed 26 minutes after dispatch, and video connection via telemedicine with a neurointensivist initiated 32 minutes after dispatch. On neurological examination she was drowsy, globally aphasic, and had partial hemianopia and a sensorimotor syndrome affecting the right side of her body. The National Institutes of Health Stroke Scale score was 19 and the Glasgow Coma Scale Score 10.

Point-of-care international normalized ratio testing was 2.2 (reported 46 minutes after dispatch), whereas complete blood counts and basic metabolic profiles were normal. Head CT (Figure) demonstrated small left thalamic ICH with intraventricular extension and ventriculomegaly. Calculated ICH score was 3. Warfarin reversal with 25 U/kg of 4-factor prothrombin complex concentrate (Kcentra, CSL Behring) was initiated in the MSTU at 57 minutes after dispatch (MSTU door-to-needle time of 40 minutes). After hospital arrival, repeat testing 106 minutes later revealed international normalized ratio normalization at 1.1. Follow-up head CT scans done at 6 and 24 hours after presentation showed stable hematoma size and she was eventually discharged to a skilled nursing facility in stable condition.

Discussion
An MSTU allows effective prehospital ischemic stroke care and can deliver thrombolytic therapy earlier compared with
standard hospital care.4 We applied this principle to ICH and were able to initiate warfarin reversal within 57 minutes of EMS dispatch, with an MSTU door-to-needle time of 40 minutes. This new treatment paradigm combining a fast-acting reversal agent with remote physician evaluation, on-site imaging, and laboratory testing for the first time affords ultra-early reversal of warfarin effect. Walter et al6 reported validation of point-of-care laboratory testing in acute stroke setting and showed reduction time to ischemic stroke thrombolysis. We are also currently correlating point-of-care test results on MSTU with hospital laboratory results.

In 2013, 4-factor prothrombin complex concentrate formulation was approved in the United States for the urgent reversal of warfarin-related acute major bleeding in adults.7 Among the advantages associated with PCC use over fresh frozen plasma are storage at room temperatures, the small infusion volume, ease of preparation and reconstitution, and rapid international normalized ratio correction (within minutes in >70% of cases).8–10 This led to the inclusion of PCC therapy in recent ICH management guidelines as a reasonable alternative for the reversal of warfarin effect.11 The recommendation was adopted at our institution in October 2013. In comparison with this case, our review of 11 ICH cases in which 4-factor prothrombin complex concentrate was used for warfarin reversal in patients admitted through the standard process of emergency department admissions or interhospital transfers to our institution found a median time from EMS activation to initiation of reversal of 150 minutes (interquartile range, 120–206.5; J.A. Gomes and C.L. Ahrens, unpublished data, 2015). A prior report on shortening the time to warfarin reversal by stroke team prenotification from the field reported median door-to-needle time of 135 minutes.12 In a hemorrhage registry, the shortest time from onset to therapy was 1 hour, but the median was 15 hours among 64 patients.13

In the largest series of mobile stroke unit deployments from Berlin, of 1455 patients evaluated, 559 (38.4%) had acute ischemic stroke and 177 (12.2%) were treated with thrombolysis in MSTU.14 The study points out the potential to treat diseases other than acute ischemic stroke. In the Berlin study, 5% had ICH and 0.3% subarachnoid hemorrhage. In acute ICH, both acute blood pressure lowering and early coagulopathy reversal are being studied.15–16 If earlier time to antihypertensive or coagulopathy reversal treatments benefits in preventing hematoma expansion, MSTU might have an important role in delivering and showing the efficacy of early hemorrhagic stroke treatment.

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**Disclosures**

C.L. Ahrens served as panel advisor for CSL Behring. The other authors report no conflicts.

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7. Product Information. **KCENTRA Intravenous Powder, Prothrombin Complex Concentrate (Human) Intravenous Powder, Kankakee, IL: CSL Behring LLC (per manufacturer); 2013.**

**Figure.** Small left posterior thalamic intracerebral hemorrhage with intraventricular extension obtained in the mobile stroke treatment unit (left) and 6 hours after warfarin reversal (right), demonstrating stable hematoma size.


Key Words: cerebral hemorrhage ■ prothrombin complex concentrates ■ warfarin
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