

Prehospital Stroke Care: Limitations of Current Interventions and Focus on New Developments

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Key Words

Stroke management · Acute stroke · Telemedicine

Abstract

Background: The global burden of stroke is immense, both in medical and economic terms. With the aging population and the ongoing industrialization of the third world, stroke prevalence is expected to increase and will have a major effect on national health expenditures. Currently, the medical treatment for acute ischemic stroke is limited to intravenous recombinant tissue plasminogen activator (IV r-tPA), but its time dependency leads to low utilization rates in routine clinical practice. Prehospital delay contributes significantly to delayed or missed treatment opportunities in acute stroke. State-of-the-art acute stroke care, starting in the prehospital phase, could thereby reduce the disease burden and its enormous financial costs. **Summary:** The first part of this review focuses on current education measures for the general public, the emergency medical services (EMS) dispatchers and paramedics. Although much has been expect-

ed of these measures to improve stroke care, no major effects on prehospital delay or missed treatment opportunities have been demonstrated over the years. Most interventional studies showed little or no effect on the onset-to-door time, IV r-tPA utilization rates or outcome, except for prenotification of the receiving hospital by the EMS. No data are currently available on the cost-effectiveness of these commonly used measures. In the second part, we discuss new developments for the improvement of prehospital stroke diagnosis and treatment which could open new perspectives in the nearby future. These include the implementation of prehospital telestroke and the deployment of mobile stroke units. These approaches may improve patient care and could serve as a platform for prehospital clinical trials. Other opportunities include the implementation of noninvasive diagnostics (like transcranial ultrasound and blood-borne biomarkers) and the reevaluation of neuroprotective strategies in the prehospital phase. **Key Messages:** Timely initiation of treatment can effectively reduce the

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medical and economic burden of stroke and should begin with optimal prehospital stroke care. For this, prehospital telemedicine is a particularly attractive approach because it is a scalable solution that has the potential to rapidly optimize acute stroke care at limited cost.

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Introduction to Acute Stroke Care

Timely treatment can effectively reduce the medical and economic burden of stroke and should begin in the prehospital phase.

Time is Brain

Rapid reperfusion of the occluded blood vessel and protection of viable but vulnerable nervous tissue in the penumbra are the two cornerstones of acute stroke therapy. The current medical treatment for acute ischemic stroke is limited to intravenous recombinant tissue plasminogen activator (IV r-tPA), but its time dependency leads to low utilization rates in routine clinical practice. International guidelines stipulate that treatment should be initiated within 4.5 h after symptom onset, yet even within this time window efficacy decreases dramatically with time, while the risk of complications increases [1, 2].

Competence is Brain

Stroke patients treated in specialized stroke units run by trained and dedicated personnel have better outcomes [3, 4]. All types of patients appear to benefit from stroke unit care [5–7] and this approach is cost-effective [8]. The European Stroke Organisation (ESO) and the American Stroke Association (ASA) recommend the immediate admission of patients with acute stroke in a stroke unit and the incorporation of a stroke unit as part of the continuum of stroke care [3, 9].

Prehospital Stroke Care

The slogans ‘time is brain’ and ‘competence is brain’ adequately point out that acute stroke is a time-critical medical emergency requiring specialized treatment. This view has largely been adopted for in-hospital patient care, but data from stroke-specific prehospital clinical trials are limited.

The primary goals of emergency medical services (EMS) for patients with suspected stroke are rapid evaluation, early stabilization, concise neurological evaluation, and quick transport and triage to the nearest medical center with a stroke unit that can provide ultra-early treatment [9–11].

In this review we aim to systematically describe the pitfalls and limitations of current prehospital strategies to reduce treatment delays. We also focus on new developments for the improvement of prehospital stroke diagnosis and we discuss therapeutic opportunities which could open new perspectives in the nearby future.

Current Strategies to Reduce Treatment Delay

Public Education

Delay in seeking medical attention after the onset of stroke symptoms often leads to missed treatment opportunities [12]. Factors influencing care-seeking behavior include psychological, cognitive, clinical, social and demographic factors [13, 14]. Multimedia campaigns generally improve stroke symptom knowledge and have been found to influence calls to EMS for stroke [15], but knowledge and awareness rapidly decrease in the months after the intervention [16]. Continuous advertising would therefore be necessary to sustain a beneficial effect. Also, these campaigns mainly target the general public and often fail to reach important risk populations [17–19]. Moreover, improved symptom awareness does not necessarily lead to increased care-seeking behavior [20, 21] and may not reduce prehospital delay or an increase in thrombolysis rates. A number of single-center studies have reported increased r-tPA treatment rates after public awareness campaigns, but these increases are difficult to attribute to these campaigns only as they were combined with multifaceted interventions such as the introduction of code stroke protocols or regionalization of stroke care [22–24]. Finally, solid evidence on the long-term effect of these interventions is lacking, as are data on their cost-effectiveness.

Education of EMS Dispatchers and Paramedics

Early identification of stroke patients by dispatchers and EMS is pivotal for rapid transport to an appropriate treatment facility. EMS dispatchers may use tools and protocols for screening via phone interview, including the Medical Priority Dispatch System [25], the Cincinnati Prehospital Stroke Scale (CPSS) [26], the Face-Arm-Speech test (FAST) [27] and the modified Los Angeles Prehospital Stroke Screen [28]. Paramedics arriving on scene are recommended to use prehospital stroke scales for the assessment of potential stroke patients. These screening tools are considered useful, despite their limited sensitivity and specificity. For instance, the false-negative rate of the CPSS and the FAST is about

24–33% [26, 27, 29]. Studies assessing the impact of these scales on transport times and treatment rates are nonexistent.

Prehospital Stroke Code Activation and Priority Transport

Priority transport to centers with adequate stroke care facilities after prehospital stroke code activation is mandatory to improve onset-to-door times. Patients transported by EMS have higher probability to arrive within 2 h of stroke onset [30], are more often treated with IV r-tPA and have better outcome [31]. Data from the Hyper Acute STroke Alarm study showed a significant increase in thrombolysis frequency and a shorter time to the stroke unit for patients with higher prehospital priority level [32]. EMS should prenotify the receiving hospital to allow in-hospital activation of the stroke protocol and mobilization of the stroke team. This reduces door-to-imaging times [33], but the effect on the door-to-needle time varies between studies [34]. Prehospital notification increases IV r-tPA administration rates by 3.2–44% [10, 35–38].

Summary

Despite major efforts, prehospital delays for stroke patients have not reduced significantly over the years [39]. Most interventional studies showed little or no effect on the onset-to-door time, r-tPA utilization rates or outcome, except for prenotification of the receiving hospital by the EMS [10, 30, 31, 35–38]. The team of Meretoja et al. [40] forms an exception; they were able to achieve median door-to-needle times of about 20 min thanks to redesigning their stroke pathways. The majority of these studies applied a pre- and postintervention design and only few randomized trials have been performed. Finally, there is no data available on the cost-effectiveness of these commonly used measures.

New Developments and Future Concepts

Telestroke

Misdiagnosis and late recognition of stroke symptoms contribute to prehospital delay and admission to inadequate clinical facilities [41]. Telestroke can bring stroke expertise to underserved geographical areas [10, 42–44] and may help solve the shortage of stroke experts [45–47] by allowing remote assessment of stroke patients via audio-video conference and by assisting local physicians in the decision-making process for acute stroke [41]. Pursuant to ongoing technological developments and in line

with the ASA and the ESO guidelines, the implementation of telestroke for optimizing in-hospital stroke care is currently applied in several countries [48–54].

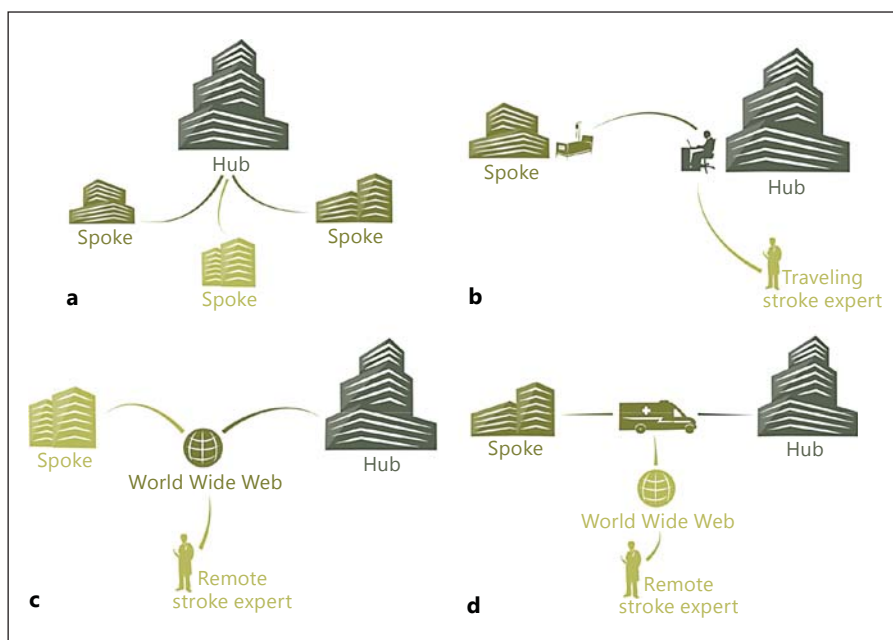
A large number of studies have shown that telestroke is a valid, accurate and reliable tool that can be used to improve stroke outcome [46, 54] and telestroke networking potentially increases the likelihood of treatment with IV r-tPA [10, 54–56]. The economic issues remain to be fully explored, but recent findings suggest that a telestroke network offers multiple benefits beyond thrombolysis [53]. It may increase the number of patients discharged home and reduce the costs borne by the network hospitals [57]. Treatment with IV r-tPA is clearly cost-effective [58, 59] and telestroke is promising to be cost-effective too, both from a hospital network point of view [57] and from a society point of view [60, 61].

Most telestroke programs are organized according to the ‘hub and spoke’ model (fig. 1a), in which a specialized center (the ‘hub’) delivers its knowledge to one or more smaller hospitals (the ‘spokes’). Technological requirements include a remote-control camera, high-resolution monitors and two-way full-motion video and audio teleconferencing [62]. The initial applications of telemedicine for stroke were hospital-based ‘point-to-point models’ over landlines (Telestroke 1.0; fig. 1b). The next generation of telestroke systems (Telestroke 2.0) used World Wide Web-based technology [63, 64], permitting consultations to be conducted from anywhere at any time (fig. 1c) and therefore leading to faster response and potentially shorter onset-to-treatment times. One of the main drawbacks lies in limited availability of high-speed internet with sufficient bandwidth [45]. Whereas ‘Telestroke 1.0 and 2.0’ were hospital-based systems aiming to provide stroke expertise to hospitals without stroke-oriented professional healthcare, ‘Telestroke 3.0’ brings telestroke to the prehospital arena (fig. 1d). Research on prehospital telestroke systems is recommended by the ASA, as it may facilitate early stroke diagnosis, the assessment of stroke severity and the selection of patients for specific stroke treatments [46].

Prehospital Telestroke

The experience with prehospital telemedicine for the assessment of stroke severity, however, is limited. Projects using bidirectional audio-video communication for real-time evaluation of patients on-site or during emergency transport are scarce, even though systems incorporating video consultation have been demonstrated to result in more accurate decision making compared to teleconsultation by telephone alone [65–67]. The TeleBAT project [50, 51] relied on mobile technology with limited

Fig. 1. **a** The ‘hub and spoke’ model connects several ‘spoke’ hospitals to 1 ‘hub’. Evolution of telemedicine applications for stroke starting from point-to-point communication over landlines between fixed workstations (Telestroke 1.0; **b**) over mobile telemedicine consultation using the World Wide Web (Telestroke 2.0; **c**) to pre-hospital telestroke care (Telestroke 3.0; **d**).



bandwidth and unstable connectivity, which completely precluded real-time conferencing. Liman et al. [68] deemed 3G connectivity to be unacceptable for clinical use because adequate assessment was possible in only 40% of the scenarios. The Aachen project [69] is currently the only project that investigated real-time prehospital telemedicine in stroke patients as opposed to healthy volunteers mimicking stroke scenarios. Broadband communication via parallelized data channels was used to mitigate the effects of unstable connectivity and dropouts, but technical instability of video transmission during ambulance transportation remained an issue. A difference in prehospital time intervals or superiority to prehospital EMS diagnosis was not proven, although the small study population could account for this. In a follow-up study, the researchers upgraded to second- and third-generation mobile networks and used roof antennas which increased video transmission performance, but stable transmission was not obtained in all cases [70]. Fourth-generation technology using ultra-broadband internet access may overcome these limitations. The Prehospital Stroke Study at the UZ Brussel (PreSSUB) showed promising results using 4G technology in healthy volunteers and allowed a more feasible and reliable assessment [71]. Although some technical issues like competition with other users for high-speed broadband access still remain to be resolved, prioritized connection for medical services could be one of the possibilities.

Standardized evaluation of stroke severity is pivotal for adequate treatment decision making. The National Institutes of Health Stroke Scale (NIHSS) is the current gold standard for bedside practice and for remote assessment by telemedicine. Even though widely used, this scale suffers from several drawbacks for use in telestroke, which inspired researchers to develop more adapted alternatives, among them being the Unassisted TeleStroke Scale [71, 72]. This scale has been shown to be a simple, quantitative measure for the evaluation of stroke severity through telemedicine, without the assistance of a third party and with a time gain of 5 min compared to the NIHSS. We have no knowledge of scales other than the NIHSS and the UTSS being tested in prehospital telemedicine to quantify neurological impairment. Scales used by (para)medics on-site to estimate prehospital probability of acute stroke could also be implemented for telestroke but lack information about stroke severity, which is important for therapeutic decision making.

Prehospital telestroke is a very promising concept, facilitating specialized stroke care in the very early stage based on integration of bidirectional audiovisual communication with point-of-care laboratory analysis, vitals and decision support software. To allow breakthrough results, several issues still need to be tackled, including data security, privacy, medical device regulations, liability on product failure and reimbursement [44, 73].

Mobile Stroke Units

An alternative view to reduce the delay to stroke treatment involves the deployment of highly specialized ambulances and stroke teams for prehospital stroke care. This approach has been evaluated in two pilot studies. Walter et al. [74] were the first to dispatch a 'mobile stroke unit' (MSU), consisting of a sizable ambulance with integrated CT scanner, point-of-care laboratory and a device for teleconsultation with the hospital neuroradiologist. The MSU is equipped with an expert team consisting of a paramedic and a physician trained in stroke medicine and is dispatched together with the standard emergency support system. Data from CT scans or real-time video of clinical examination of patients were transmitted via High-Speed Downlink Packet Access. MSU care was associated with a significant reduction in the time from alarm to treatment decision compared to optimized conventional stroke treatment, but this did not result in a higher number of patients receiving thrombolytic therapy or in improved neurological outcome [74]. The deployment of a stroke emergency mobile unit (STEMO) has been tested in the Pre-Hospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) study [75]. Similar to the MSU, the STEMO was equipped with a neurologist, a radiologist, a paramedic, a CT scanner, a point-of-care laboratory, and a teleradiology system. Prehospital diagnostics were performed on-site or in the STEMO. Images of a CT brain scan were sent to a radiologist on call via a teleconsultation system using a 3G connection. In contrast to the MSU, the PHANTOM-S study was conducted in a densely populated area and a radiologist was present in the STEMO. This study showed that it is feasible and safe to identify acute stroke patients and to administer thrombolytics in the prehospital arena. Moreover, this intervention was associated with a significant reduction of the call-to-needle time compared to controls [75]. However, scalability and radiation legislation limit the widespread application of this strategy. The price tag of integrating CT scans into emergency vehicles and the staffing costs for the accompanying highly trained personnel are likely to limit wide implementation. Data on the cost-effectiveness of this approach are currently lacking.

Prehospital Transcranial Ultrasound

Being noninvasive, nonradiating and less expensive than other imaging techniques, ultrasound has been evaluated in the prehospital setting in various conditions [76–78]. Its feasibility was firstly documented in the Regensburg stroke mobile project [77]. Several drawbacks cur-

rently limit the implementation of this technique. Firstly, the use of 2-mHz transcranial Doppler and duplex should be validated for cloth localization. Secondly, the use of contrast agents to enhance sensitivity of ultrasound devices is currently not approved in the USA. Thirdly, the value of pulsatility monitoring to discern hemorrhagic presentations would need to be explored. Fourthly, scanning protocols would need to be established and validated. Finally, a trained sonographer would be required on-site. As currently very few practitioners have developed skills in transcranial ultrasound, this limits the generalizability of this approach.

Blood-Borne Biomarkers

The diagnostic and prognostic value of numerous biochemical substances reflecting various aspects of the ischemic cascade have been studied [79], but until now no biomarker with sufficient specificity and sensitivity has been identified to justify its use in routine clinical practice. Measurement of E-selectin and resistin have shown additive value to traditional risk factors [80]. Plasma glial fibrillary acid protein analysis has shown the ability to differentiate intracranial hemorrhage and ischemic stroke within 4.5 h of symptom onset, and point-of-care systems could be useful in the prehospital phase [81]. The identification of biomarkers with adequate diagnostic accuracy, which can readily be measured with limited cost, could prove to be a major breakthrough in acute stroke management.

Neuroprotective Strategies

Despite showing efficacy in experimental models, the concept of neuroprotection has failed in clinical trials. Several reasons have been identified for the translational difficulties faced by the numerous neuroprotective strategies tested over the last two decades, but delayed initiation of the treatment has been a major contributor in the overwhelming majority of trials [82]. Because the beneficial effects of neuroprotection are likely to be more pronounced if initiated early, it is reasonable to reexamine the most promising agents in the prehospital phase of acute stroke.

The Field Administration of Stroke Therapy – Magnesium (FAST-MAG) trial puts this approach to test. This ongoing phase III neuroprotection trial evaluates the effectiveness and safety of field-initiated magnesium sulfate in improving the long-term functional outcome of patients with acute stroke [83]. Magnesium acts as a natural calcium blocker and may therefore inhibit or delay calcium-mediated ischemic cell death during and after cere-

Table 1. Overview of new developments for improvement of prehospital stroke care

Approach	Research projects	Features	Challenges
Prehospital telestroke	TeleBAT [50, 51] Liman et al. [68] Aachen project [69] PreSSUB [71]	Bidirectional audio communication Uni- or bidirectional video communication Real-time clinical evaluation Real-time transmission of vital parameters Prearrival notification Relatively low implementation cost Stroke history checklist (Aachen project) ECG transmission (Aachen project) Independent of location consultant (PreSSUB)	Dependence on mobile internet connection No brain imaging prior to arrival at hospital Data on time-to-treatment decision are not yet available Diagnostic superiority to standard care is not yet established
MSU	MSU [74] STEMO [75]	On-site presence of physician trained in stroke Integrated CT scan and point-of-care laboratory Teleneuroradiology or radiologist on site Reduction of time-to-treatment decision has been demonstrated	Lack of scalability with high implementation cost Specialized staff required on-site at all times Radiation legislation Access to 3G required for teleradiology Real-time images are not available Increased r-tPA utilization or improved outcome remains to be demonstrated
Prehospital trans-cranial ultrasound	Regensburg project [77]	Noninvasive and nonradiating imaging Low implementation cost Diagnosis of middle cerebral artery occlusion	Trained neurosonographer required on site Validation studies are required Contrast agents are not widely approved
Blood-borne biomarkers	Glial fibrillary acid protein [81]	Differentiation between ischemic and hemorrhagic stroke is plausible	Low sensitivity and specificity Point-of-care system unavailable Not yet evaluated in the prehospital setting
Neuroprotective strategies	FAST-MAG [83] Minocycline [85]	Possible neuroprotective effects Reassuring safety profile	Early administration is mandatory Data from FAST-MAG are not yet available Minocycline has not been shown to be efficacious

bral ischemic events [84]. Very early initiation of neuroprotective support could help to preserve the penumbra until recanalization therapy can be started [83].

Agents targeting inflammation, like minocycline, may also prove to be beneficial as neuroprotective agents. In a recent pilot study the use of intravenous-administered minocycline in a small sample of acute ischemic and hemorrhagic stroke patients has proven to be safe but not efficacious [85], although scalability and a relative delay in administration (within 24 h after onset) could account for this.

Potential Impact of New Developments

The new strategies described above hold the potential to improve patient outcome as they may reduce the time to stroke care by initiating the diagnostic and the therapeutic processes already on-site or during ambulance transportation. These approaches may also augment the rate of thrombolytic therapy and improve patient selection for advanced treatment in specialized centers. Further, prehospital telestroke and MSU are uniquely situated as platforms for the administration of neuroprotective agents very early in the prehospital phase, aiming to

preserve the penumbra while awaiting recanalization therapy [83]. This would offer ample opportunity to boost research in this field, including expedited administration of (new) therapies, enhancement of inclusion rates, facilitation of informed consent procedures, and improved overall research quality thanks to real-time involvement of stroke experts and post hoc case reviewing using recordings of the telestroke consultations [47]. Hypothermia, statins, minocycline, magnesium sulfate and albumin are examples of neuroprotective treatments that could make suitable candidates for prehospital clinical trials supported by emergency telestroke consultation or MSU. The advantages and disadvantages of these new developments are summarized in table 1.

Conclusion

The concepts ‘time is brain’ and ‘competence is brain’ have shifted the focus of acute stroke care to providing specialized support already in the prehospital arena. Education-based programs have been demonstrated to be insufficient in reducing missed treatment opportunities.

Much is expected from prehospital telemedicine, which opens new perspectives and may allow continuous guidance by a stroke specialist throughout the acute stroke care continuum. Deployment of MSU could be an alternative in densely populated regions with ample access to highly trained caregivers and without stringent budgetary restrictions. Other opportunities include the implementation of noninvasive diagnostics, reevaluation of neuroprotective strategies and improved quality of clinical trials in the prehospital setting.

Disclosure Statement

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