REVIEW ARTICLE

Factors associated with pre-hospital delays in patients requiring treatment for ischemic stroke.

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Abstract

Cerebral ischemic stroke is the leading cause of death and adulthood disability in developed countries such as the UK and USA. The only pharmacological treatment available is intravenous thrombolytic therapy, which is most effective and beneficial to patients when administrated within a relatively short time window following stroke onset. However, a large number of patients are ineligible for thrombolysis treatment due to delays in receiving treatment. In this review we discuss those factors which are associated with treatment delay. Understanding such factors that contribute to treatment delays, especially in different regions of the world, may help to improve the time at which treatment can be delivered to stroke patients and reduce the detrimental effects of stroke.

Keywords: ischemic stroke, treatment, delay, global.

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Introduction

Stroke is the third leading cause of mortality and the leading cause of neurologic disability in most developed countries, such as the UK and USA (1). However, stroke is also a serious health issue in developing nations, for example, in Taiwan, China, it has been the second leading cause of death since 2000. In 2014, the WHO Global Status Report on non-communicable diseases listed stroke as one of the leading causes of death and adult disability worldwide (2). Thus, access to appropriate treatment for stroke is a serious priority for medical institutions and health organizations worldwide.

The majority of cerebral strokes are ischemic in nature, resulting from the occlusion of a major cerebral artery by a thrombus or embolism (3). Restoration of blood flow, by pharmacological or surgical means, is critical for limiting the impact of the stroke on brain function. Pharmacological thrombolytic treatment, via intravenous tissue plasminogen activator (t-PA) has been shown to be highly effective in reducing death rates following stroke and improving long-term prognosis (2). Thrombolytic t-PA treatment has shown to be most effective when administered within the first 3 hours following symptom onset for ischemic stroke (4), and the earlier the treatment is given, the greater the benefit (5-6). This is probably because the longer the delay between symptom onset and receiving treatment, the lower the chance of restoring blood flow and the higher the risk for hemorrhage complications (7). Thus, intravenous thrombolytic therapy is not recommended beyond its therapeutic time window due to the high risk of cerebral hemorrhage and poor neurological outcomes (7-8). Unfortunately, more than 70% of ischemic stroke patients present outside the 3-hour window of t-PA eligibility worldwide, and approximately only 5% of ischemic stroke patients go on to receive t-PA (9-10). Thus, it is timely to consider those factors which may contribute to pre-hospital delays in order to further understand the global problem of late arrival for ischemic stroke treatment.

Pre-hospital delays in seeking treatment – a global problem?

The most effective time window for receiving effective thrombolytic t-PA treatment is typically 3 hours thus, many studies reported here use either 2 or 3 hours post-symptom onset as a cut-off point for receiving t-PA treatment. Acute ischemic stroke, in the majority of medical centers, is accurately diagnosed by clinical examination and neuroimaging, and patients should have undergone at least one brain scan by CT or MRI to aid diagnosis (11).

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Asia

According to data retrospectively collected from the medical records of 247 ischemic stroke patients presenting to a metropolitan university hospital over a one-year period in Seoul (Korea), only 18.2% of patients arrived in the emergency room within 2 hours of symptom onset (12). In Shanghai, the largest and most developed region of China, 30.2% of ischemic stroke patients (13) presented within 3 hours of symptom onset, a finding similar to a study conducted in Taiwan (China), with 28% patients arriving at the hospital within 2 hours of onset (13). In Japan, smaller-scale studies report that 41% ischemic stroke patients arrive within 3 hours of initial symptom onset (14) although levels in Taiwan are reported to be as high as 72% of ischemic stroke patients presenting within 2 hours of symptom onset (15). However, all of these studies are single-hospital taking place within an advanced medical center for that particular region that may serve a population of up to 3 million people. Such centers are chosen for study as they have the resources to administer t-PA to ischemic stroke patients, which in Asia, is not commonplace in all medical centers. To try and overcome this limitation a large-scale study took place in China which interviewed and reviewed the medical records of ischemic stroke patients from 66 hospitals in 13 major cities across the Hubei Province, a province in China with a slightly lower level of economic development compared to Shanghai (2). The 66 hospitals included varied in speciality, size, and location (for example, urban or rural) but all had the resources to administer intravenous thrombolysis therapy to ischemic stroke patients. In that study, 69.3% of ischemic stroke patients took longer than 3 hours to seek hospital treatment meaning 30.7% of patients arrived within 3 hours. Interestingly, 55.3% of patients took longer than 6 hours to seek hospital treatment. All studies in Asia were conducted in a retrospective form, in which data were acquired through interview, questionnaires and review of medical records collection. Errors may have occurred by medical staff and researchers reviewing the records.

Europe

In Europe various prospective studies have been conducted and tend to report better rates in terms of the percentage of ischemic stroke patients reaching hospital within 3 hours compared to the studies conducted in Asia. For example, in a prospective study, conducted in a large-scale hospital serving as both a tertiary and reference center for t-PA usage in Turkey, 72.6% of patients arrived at any hospital within 3 hours from the notice of symptoms (16). In order to receive t-PA treatment patients had to be received or transferred to the Karadeniz

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Technical University Medical Faculty Hospital assigned in the study and 48.7% of ischemic stroke patients did so within 3 hours. In another example, a prospective study conducted in Spain, found that 39.2% of stroke patients presented in less than 3 hours (17) although their study was not restricted ischemic stroke patients and also included patients later diagnosed with intracerebral hemorrhage, transient ischemic attack, and cerebral infraction (CI). In a larger scale study conducted in Germany the median (because of a skewed data distribution) was 151 minutes with approximately 50% of patients arriving at hospital between 2 and 3 hours following symptom onset.

North America

In North America there are marked regional differences in the time, on average, patients are arriving at hospital to seek treatment for stroke symptoms. For example, a retrospective study conducted in Chicago reported that 31.6% patients arrived at hospital within 2 hours following symptom onset although the study was conducted in a single hospital with a relatively small sample size (18). In a multi-center study conducted in Michigan, involving almost two thousand patients, 19% of ischemic stroke patients arrived at hospital within 2 hours of symptom onset with 59% patients taking longer than 6 hours to arrive (19). In a nationwide study, involving 35 academic USA medical centers participating in the University HealthSystem Consortium Ischemic Stroke Benchmarking Project (2001-2004), a third of all patients arrived within 2 hours from symptom onset (20).

What factors contribute to pre-hospital delays?

Previous medical history

It is important to consider which factors might contribute to delays in patients seeking hospital treatment. It may be that if a patient has prior experience of a stroke, or other medical complication, they are more likely to seek hospital treatment quicker. For example, studies conducted in Shanghai and Taiwan (China) found that ischemic stroke patients with a previous history of stroke had significantly less time-to-hospital delay than those without a previous history (11, 21). Such a finding might indicate that the relatives or carers of those patients with a stroke history might have more knowledge and awareness of both stroke symptoms and the potential impact of a stroke. Elderly patients with chronic neurological diseases such as dementia, progressive cardiac, or pulmonary disease were significantly less likely to arrive at hospital early (12) although that is probably due to difficulties associated with transporting such patients. Although some studies report that

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previous medical history does not help reduce the delays associated with hospital arrival for ischemic stroke patients. In studies carried out in Turkey and China, no significant differences were observed between the early and later arrival groups in terms of whether there was any previous history of stroke (16, 22). This was also the case, i.e. no difference, if patients had a previous history of hypertension, diabetes, hyperlipidemia, or congestive heart failure. In agreement, a study by Turan et al (23) found that a patients previous history of stroke (including family history of stroke), myocardial infarction, congestive heart failure, prosthetic heart valve, hypertension, and diabetes were not significantly associated with arrival time. However, univariate analysis shows that patients with a medical history of coronary artery disease and dyslipidemia were statistically more likely to arrive earlier than patients with no history of such illnesses (23). Although it's worth noting that patients arriving at hospital with underlying conditions such as hypertension or other noncomitant emergency conditions may require some management of those and therefore delay onset of stroke treatment (24).

Stroke type, severity and symptoms

The National Institute of Health Stroke Scale (NIHSS) characterises the neurological deficit resulting from stroke (16), and the higher the NIHSS score, the less favorable the outcome. Not surprisingly, those stroke patients associated with a higher NIHSS score tend to arrive earlier to hospital in order to seek treatment (11, 16, 17, 23, 25). Interestingly, stroke type seems to also play a role in the time patients take to seek treatment, for example, patients experiencing a transient ischemic attack (TIA) or hemorrhagic stroke are more likely to arrive at hospital within two hours of symptom onset compared to those experiencing an ischemic stroke (17, 19). In addition to stroke type and severity, the nature of the symptoms also seems to affect the time patients take to seek medical attention. Stroke symptoms can be diverse and include those which are considered stroke-specific, such as hemi body paraesthesia, hemiparesis, ataxia, speech/language disturbance, as well as those symptoms which are less specific to stroke and may include neurological (for example, mental status change, migraine) and non-neurological (for example, chest pain, shortness of breath) symptoms. Loss of consciousness has been found to be significantly associated with earlier arrival of ischemic stroke patients (16), probably because carers/bystanders are likely to call emergency services (14). Those ischemic stroke patients, where no loss of consciousness is experienced, tend to be amongst the group of stroke patients taking longest to seek medical care (11). Of course, in elderly patients who

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are more likely to live alone loss of consciousness may actually the delay time for seeking medical attention (19).

In addition to loss of consciousness, patients experiencing a motor symptom (e.g. loss of function) were more likely to seek treatment quicker than those not experiencing changes in motor ability (26). Numbness or weakness tend to be associated, in ischemic stroke patients, with earlier arrival following symptom onset, whereas visual disturbances, non-specific pain and changes in balance tend to be associated with later arrival times (19). In addition to the type of stroke symptom, the nature of the stroke symptom, in terms of whether progressive or static, has also been found to significantly impact upon time taken to seek medical attention. For example, a study conducted in Korea, reported that patients were morel likely to delay seeking medical attention if their symptoms appeared progressive, i.e. worsening over time, than those patients in which symptoms appeared more static (12). Of course this is probably related to the severity of the symptoms in that progressive symptoms may present gradually and worsen over time whereas static symptoms may present as relatively severe from the onset. In addition, the ability of the patients and their carers/bystanders to recognize stroke symptoms and understand the urgency for seeking treatment may also impact upon the time taken to seek medical attention. Countries such as the UK and USA have run public health campaigns, such as 'FAST' (facial weakness, arm weakness, slurring of speech, time to call emergency assistance), aimed at encouraging the public to recognise stroke symptoms appropriately and to seek timely medical attention. Some studies have conducted questionnaires in order to assess the ability of relatives and/or carers of ischemic stroke patients to identify the severity of stroke symptoms and the need to seek urgent medical care. Significant decreases in the time taken to reach hospital following symptom onset were found in those stroke patients who were with individuals better able to recognize and identify stroke symptoms (16). Such an effect was enhanced if they had first-hand knowledge of another individual experiencing an ischemic stroke (27).

Age and education

There is conflicting data as to whether age affects the delay patients may experience in seeking medical attention for ischemic stroke. For example, in some studies, age was found to be significantly associated with increased pre-hospital delay (12) whereas others report increased age reduces delay (15, 27). In those studies, reporting increased delays in older patients if the data is separated into those experiencing a pre-hospital delay (i.e. taking

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more than 3 hours to seek medical care) and those not the mean age of the delayed group was significantly higher than the non-delayed group and the delay in seeking medical care was significantly increased in those aged over 65 years (12). However, other studies report that increasing age of patients was more likely to result in use of emergency services and therefore shorten the time between symptom onset and arrival at hospital (28). In terms of other factors, some studies report that educational level is an independent factor affecting pre-hospital delay. The lower the educational level, the longer the time had spent between symptom onset and arrival for medical attention this may be due to a lack of awareness or misjudgment of the seriousness of symptoms (15, 29-31).

Geographical location at time of stroke onset

In those studies which take into account the geographical location at the time of stroke onset, it appears that if the stroke occurs at a location away from home this is associated with a significant decrease in the time taken to seek medical attention (17) and onset of ischemic stroke at home was significantly associated with ischemic stroke patients taking more than 3 hours to seek medical attention (2). Of course, it is probable that onset of stroke in a workplace or other public settings increases the number of potential witnesses who can recognise, and act upon, the possibility of a stroke occurring. In some instances patients are transferred between, for example a community-based hospital, to an emergency-care hospital in order that t-PA treatment may be administered and this may both reduce and increase treatment delays depending on the efficiency of transferring patients between medical institutions (2, 12).

Use of emergency services

Nearly all studies report the important role that Emergency Medical Services (EMS) can play in reducing pre-hospital delays. Patients who called EMS and used ambulance transport were found to have earlier arrivals compared to those who did (27, 28). For example, calling the emergency number 120 was independently associated with shorter pre-hospital delays in China and calling 911 was a significant predictor of a delay shorter than 2 hours. It is also likely, that the use of EMS decreases the time taken for the patient to be seen by an emergency physician, to undergo a CT scan and to receive a consultation by a neurologist. All of these factors have to occur for a definite diagnosis of ischemic stroke to take place and eligibility for t-PA treatment considered.

Conclusions

Evidence has shown that there are various factors contributing to pre-treatment delays for

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ischemic stroke patients. However, such factors may vary between, and even within, countries or regions and should therefore be considered when developing educational and public health campaigns. In addition, government and public health bodies in both developed and developing countries should consider how to improve community-based medical systems, emergency transport networks, and ensuring, where relevant, improved access to thrombolysis treatment.

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