A RETROSPECTIVE ANALYSIS OF TIME DELAYS IN PATIENTS PRESENTING WITH CEREBROVASCULAR ACCIDENT (STROKE)

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Radiology.

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Declaration

I, Diteboho Khalema, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (Diagnostic Radiology) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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17th Day of February 2017

Dedication

This work is dedicated to my family; mum and dad- Lineo and Mosehle Khalema, for always cheering me on, my siblings Naledi and Mmathabiso, for always setting the bar high, I look up to you.
To my son, Kutlwano Khalema, my constant inspiration.

Publications and Presentations

This work has never been published nor presented at any local or international congress.

ABSTRACT:
OBJECTIVES:

1. To determine the time to presentation to the Emergency Department for patients presenting with stroke

2. To determine time from ED arrival to CT for patients presenting with stroke

3. To determine factors influencing the time to presentation.

4. To determine the number of patients who received or who could have potentially received thrombolysis for stroke in our setting.

METHODS: Retrospective record review of time intervals regarding symptom onset, ED presentation and time to CT scan were recorded in patients who presented to the ED with signs and symptoms of stroke in 2014.

RESULTS: There were 232 patient records included in the study. The average time to presentation to the ED was 33 hours with only 13.7% presenting within 3 hours. The earliest presentation was within 30 minutes of the onset of symptoms and the most delayed presentation was 3 months. Factors associated with early presentation were female sex, smoking and loss of consciousness. Known diabetic patients presented later than non-diabetic patients. Seventy-five percent of stroke patients had an ischaemic stroke and 25% were haemorrhagic.

CONCLUSIONS: Due to delays in presentation, despite the availability of thrombolysis, patients are still not receiving thrombolytic treatment.

Acknowledgements

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GLOSSARY OF ABBREVIATIONS

AHA	American Heart Association
ASA	American Stroke Association
ASPECTS	Alberta Stroke Program Early CT Score
AVM	Arterio-Venous Malformation
BI	Barthel Index
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CNS	Central Nervous System
CT	Computed Tomography
CTA	Computed Tomography Angiogram
DWI	Diffusion Weighted Imaging
ECASS	European Cooperative Acute Stroke Study
ED	Emergency Department
EMEA	European Medicines Evaluation Agency
EMS	Emergency Medical Service
EXTEND	Extending the time for thrombolysis in Emergency Neurological Deficits
FDA	Federal Food and Drug Association
GCS	Glasgow Coma Scale
IST-3	The Third International Stroke Trial
MCA	Middle Cerebral Artery
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale

MTT	Mean Transit Time
NINDS	National Institute of Neurological Disorders and Stroke
OHS	Oxford Handicap Scale
PACS	Picture Archiving and Communication System
ROI	Region of Interest
TPA	Tissue Plasminogen Activator

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Chapter 1 INTRODUCTION

Motivation and rationale for this research

Stroke is a common presentation in the Emergency Department (ED). The effects of stroke can be devastating for the patient and his/her family due to the mortality and morbidity associated with it. The residual impairments, sometimes permanent, can lead to serious consequences such as an inability to work, loss of income and patients becoming completely dependent. In a developing country, follow-up and rehabilitation is a challenge especially in a resource-constrained environment where basic needs are already limited. Social circumstances that a patient is being discharged into, such as: no primary caregiver, a house with no running water, no electricity, overcrowding or poor nutrition may all contribute negatively to rehabilitation. Studies have shown significantly poor rehabilitation outcomes in stroke patients due to their socio-economic circumstances. Chest infections, pressure sores and hypoglycaemia are but some of the complications that were responsible for the high morbidity and mortality rates reported(1, 2). De Villiers et al found that shack housing was related to bad outcomes in stroke patients that were followed up 6 months after being discharged from a hospital in Cape Town(1).

With the changes in lifestyle and diet, South Africans are now at higher risk of developing diseases such as stroke earlier than before(3, 4). Primary prevention should be the main focus in the management of stroke in any environment. Identifying those patients that are at risk of developing a stroke, implementing lifestyle changes and optimising treatment in diseases such as hypertension, diabetes and hypercholesterolaemia can be done in a local clinic setting. Once a patient develops an ischaemic stroke, treatment should be initiated as soon as possible. Patients should receive thrombolysis within 3 hours, or 4.5 hours if they meet the exclusion criteria(5, 6). This limited therapeutic window poses a significant challenge particularly in poor socio-economic circumstances, which most of our patients, who rely on public transport, find themselves in.

Stroke can be divided into ischaemic and haemorrhagic. It is important to determine the type of stroke a patient has in order to decide what management to undertake. Although certain clinical signs and symptoms -depending on the severity- can suggest the subtype of stroke, the final

diagnosis can only be confirmed by appropriate neurological imaging(7). Stroke symptoms vary from aphasia, facial paralysis, hemiplegia/hemiparesis, convulsions to decreased level of consciousness, these are all symptoms that can be identified by a non-medical/lay person who can therefore make a decision to seek urgent medical care(8,9,13).

Dedicated stroke units with a stroke team have been shown to improve stroke patient care by reducing waiting times and initiating treatment as soon as possible(14-17). Even patients with a haemorrhagic stroke, where thrombolysis is not indicated, have better outcomes in a stroke unit(1). Currently only a few dedicated stroke centres exist in South Africa- most of them in the private sector.

Statement of the problem

Stroke is a debilitating disease that not only affects the patient physically, but can lead to serious financial burden for the patient and the family. Stroke is both preventable and can be treated. Despite the availability of Alteplase(t-PA), which as been proven to improve clinical outcomes of patients with ischaemic stroke, there are still low rates of thrombolysis. This study sought to evaluate and analyze the times associated with patients presenting with stroke to the ED at the Helen Joseph Hospital.

Study Objectives

Primary Objectives:

1. To determine the time to presentation to the ED for patients presenting with stroke
2. To determine time from ED arrival to CT for patients presenting with stroke

Secondary Objectives:

3. To determine factors influencing the time to presentation.
4. To determine the number of patients who received or who could have potentially received thrombolysis for stroke at the Helen Joseph Hospital ED.

Chapter 2 LITERATURE REVIEW

Introduction

Stroke is one of the top 10 leading causes of disability in the world and a serious cause of mortality in South Africa(2, 18). Seven hundred and ninety five thousand people in the United States are diagnosed with a stroke each year, with about 75% of these as first episode and 25% recurrent. One in 18 deaths in the United States can be accounted for by stroke with someone having a stroke every 40 seconds(19). In South Africa, ischaemic strokes contribute to 85% of all strokes and haemorrhagic strokes 15%(18). Stroke is third leading cause of death in the world, following neoplastic diseases and ischaemic heart disease (20).

Eighty per cent of strokes are preventable. Stroke causes a serious financial burden on society; this not only includes the acute treatment of the stroke but also rehabilitation and may also imply loss of income for the patient(21). In the United States it is estimated that the cost of stroke will increase by 129%, with an estimated 3.4 million more people (4% of the United States adult population) developing a stroke by 2030(21). Emphasis should be on primary prevention, modifying risk factors in patients that are at risk and early presentation to the ED once a patient develops stroke symptoms.

The American Heart Association/American Stroke Association (AHA/ASA) define a Central Nervous System (CNS) infarction as “more than 24 hours of ischaemic symptoms or imaging showing ischaemic pathology in a particular vascular distribution”(19). Previously, stroke was only treated conservatively. This included airway, blood pressure and blood glucose monitoring, physiotherapy and rehabilitation. In June 1996, after the National Institute of Neurological Disorders and Stroke (NINDS) published results of a prospective and double-blind randomised, placebo controlled trial, the Federal Food and Drug Association (FDA) approved thrombolysis with Alteplase as the first ischaemic stroke treatment(5, 23).

Definitions in stroke:

Transient Ischaemic Attack (TIA)

Defined as a focal neurological event that typically lasts less than one hour with no associated imaging abnormalities found(24). This poses a management dilemma as an ischaemic stroke in

the hyperacute stage may also present with normal CT findings. It has been shown to lead to a stroke and therefore should be treated as a medical emergency(25).

Ischaemic Stroke

Pathological or imaging features in a particular vascular territory or clinical features that persist for more than 24 hours or until death other aetiologies excluded(22).

Haemorrhagic Stroke

Neurological dysfunction that develops rapidly due to a focal collection of blood within the parenchyma or ventricles(22). The most common areas affected are the basal ganglia, thalamus, cerebellum and pons(26).

Subarachnoid haemorrhage

Blood within the subarachnoid space (the space between the arachnoid and pia mater). The patient usually presents with headache and neurological signs(22).

Thrombolysis:

History

Activation of the fibrinolytic system was first described in the 1930s when substances made from bacteria, tissue and urine (streptokinase and staphylokinase, fibrinokinase and urinokinase respectively) or bat saliva were seen to activate it(27). The initial use of plasmin for treatment of an ischaemic stroke was first reported in 1958(28). Appropriate patient selection was not possible until the advent of CT in the 1970s(27). Initially streptokinase was used, but due to its lack of fibrin specificity, it was unsuccessful and instead was associated with increased intracerebral bleeding and an increase in mortality(27, 29). The discovery of recombinant t-PA was not until 1979. This was associated with better results and less side effects(27). The production of recombinant t-PA (Tissue Plasminogen Activator) began in 1983. So began the initiation of clinical trials for thrombolysis, however it was mainly for coronary artery occlusion(27).

Three-hour window period

Various studies followed thereafter to assess the efficacy of intravenous t-PA for thrombolysis in acute stroke. In 1995 the NINDS t-PA trial was the first trial to demonstrate improved

neurological outcome when patients were treated with thrombolysis within 3 hours of stroke onset(5). There was a higher rate of symptomatic intracranial haemorrhage in the t-PA group compared to the placebo group (6.4% vs 0.6%) but no difference in mortality was noted(5). Six months after the NINDS results were published, the use of IV t-PA for acute ischaemic stroke within 3 hours of symptom onset was approved by the FDA for the first time(5, 6).

Table 2.1 The recommendations for door to needle time in treating stroke patients(30):

0 minutes	ED arrival
<10 minutes	ABC, Vital signs, Oxygen as needed, Glucose and ECG
<25 minutes	Neurologic assessment/ Stroke team and book CT scan
< 45 minutes	CT scan Interpretation
<60 minutes	Thrombolytic therapy to be given

Patients should be treated within the 3 hour window period(23).

However, there is still controversy that exists against the use of Alteplase for stroke. The efficacy is questioned in cases where a patient is treated inappropriately leading to severe intracranial haemorrhage and death in a patient who may have done better with conservative treatment(31).

The following are recommendations by the AHA/ASA for thrombolysis:

- Ischaemic stroke with neurologic signs
- Symptoms less than 3 hours
- Patient older than 18 years of age
- No significant head trauma or stroke in the past 3 months
- No symptoms suggesting a subarachnoid haemorrhage
- No arterial puncture in a site that cannot be compressed in the previous week
- No previous intracranial bleed

- No previous gastro-intestinal or genitourinary bleed in the past 3 weeks
- No intracranial tumour, AVM or aneurysm
- No history of recent neurosurgery (Brain or spinal)
- Systolic blood pressure less than 185mmHg or diastolic less than 110mmHg
- Acute bleeding disorder including: thrombocytopenia, platelets of less than 100 000/mm
- Elevated aPTT secondary to heparin injection 2 days prior
- Hypoglycaemia, blood glucose < 2.7mmol/L
- Large infarct CT hypo density of >1/3of the cerebral hemisphere (32)

Where the benefit outweighs the risk, patients with certain contraindications may receive thrombolysis:

- Minor or rapidly improving symptoms
- Pregnancy
- Seizure at stroke onset with persistent neurological signs
- History of trauma or surgery in the past 2 weeks
- Previous gastro-intestinal or genitourinary bleed in the past 3 weeks
- Myocardial infarct within the past 3 months(32)

Extended window period

Other studies investigated a longer time period for thrombolysis namely the European Cooperative Acute Stroke Study (ECASS-I(1995) and ECASS II(1998))(33, 34). ECASS II used a lower dose of alteplase(0.9mg/kg) compared to ECASS I (1.1mg/kg) and also modified the CT exclusion criteria(33). The conclusion showed improved clinical outcomes at 3 to 6 hours however there was also an increase in symptomatic intracranial haemorrhage but no significant mortality rate seen between the t-PA group and the placebo group(6, 33).

ECASS III (2008) showed a good outcome at 3 to 4.5 hour window period, however certain exclusion criteria had to be met. The exclusion were patients over the age of 80, NIHSS>25(35, 36), use of oral anticoagulants regardless of coagulation results, history of previous stroke and known diabetic patients(37). In the Third International Stroke Trial (IST-3), 53% of the participants were older than 80. This study showed improved clinical outcome in all patients thrombolysed with r-tPA within 3 hours regardless of their age(38). In 2009 the AHA/ASA recommended the extended time period with the ECASS III exclusion criteria(39). In 2010,

following the ECASS-III study, the European Medicines agency (EMEA) approved the extended time period between 3 to 4.5hours(6).

Ongoing studies

Currently ongoing studies (ECASS IV and EXTEND(Extending the time for thrombolysis in Emergency Neurological Deficits)) will include patients who woke up with symptoms therefore (unknown time of stroke onset) and patients with symptoms between 3 and 9 hours after stroke onset(6, 40). With improvements in penumbral imaging and other modalities there is a further possibility of safely selecting more patients for the extended time period(6).

Even with the current extended time period or even more extended time periods being investigated, patients with no contraindications that qualify for thrombolysis should be treated as early as possible. Class 1 evidence shows that treatment should be started within an hour of arrival to hospital(32). The earlier patients are treated the better the outcome(41, 42). Saver et al showed that even 15 minutes made a difference(32). With every 15 minute delay to thrombolysis, patients are less likely to be discharged home walking(41), and are more likely to have intracranial bleeds and die in hospital(42).

Imaging in stroke

Imaging plays a pivotal role in the management of stroke, namely to exclude a haemorrhagic stroke that is an absolute contraindication for thrombolysis and in excluding stroke mimics(43). Multiple imaging modalities are available for stroke. These include non-contrast Computed Tomography (CT), Computed Tomography Angiogram (CTA), CT Perfusion Studies and Magnetic Resonance Imaging (MRI).

Early CT signs:

Loss of insular ribbon sign

In a Middle Cerebral Artery (MCA) infarct, the insular cortex becomes the area of the brain furthest from anterior and posterior cerebral collateral blood flow and therefore becomes the area most sensitive to an MCA infarct(41). The imaging appearance is a loss of the normal gray-white matter interface in the insular cortex due to intracellular oedema(43, 44).

Obscuration of the lentiform nucleus

The basal ganglia is supplied by the lenticulostriate branches that are end-arteries causing it to be particularly vulnerable to an early infarct. This sign is also seen due to cytotoxic oedema, may be seen as early as 2 hours post onset of symptoms (43, 44, 45).

Hyperdense MCA sign

High attenuation in the MCA on a non-contrast CT is very sensitive to an early infarct. False positives may arise due to a high haematocrit level and artherosclerosis(43, 47).

These signs may be very subtle in a patient that is scanned early and should specifically be sought, however, the main aim in performing a CT scan in these patients is to exclude bleeds and mass lesions which would be a contraindication for thrombolysis(43). Narrowing the window width and center on CT improves the sensitivity of stroke detection, therefore making it easier to detect strokes that would otherwise be difficult to detect on standard brain window settings(46).

Subacute stroke

Subacute strokes are made more easily identifiable on CT as they are characterised by vasogenic oedema, hypoattenuation and mass effect but by this stage, patients would have exceeded the time frame for thrombolysis and therefore not be eligible for treatment(43).

Chronic stroke

Hypoattenuation with loss of brain volume(43). Unenhanced CT remains the modality of choice due to availability and time.

In some institutions the "Alberta Stroke Program Early CT Score (ASPECTS)" is used where the MCA territory on an axial CT is divided into 10 to assess the severity and therefore the prognosis of stroke, for every region affected a point is deducted thus the lesser the score the poorer the prognosis(46, 48). This may be useful to the clinician on deciding which patients to thrombolyse.

CT angiography (CTA)

CTA assists in visualising intra- and extracranial carotid vessels and may directly visualise the

clot. It can also help identify other causes for stroke such as a carotid artery dissection, stenosis, aneurysms and arterio-venous malformations(44, 46).

CT Perfusion imaging

Perfusion imaging is based on the concept of the ischaemic penumbra that was initially described in 1981 by Astrup et al as a peripheral area of focal cerebral ischaemia where blood flow is reduced enough to cause hypoxia and arrest physiological function but has the capacity to recover if perfusion is improved(49, 50). Perfusion imaging can be added onto most modern CT scanners and allows non-invasive, quick evaluation of cerebral perfusion, ischaemia and infarction(43).

Based on measuring the following parameters Cerebral blood flow (CBF), Cerebral blood volume (CBV) and Mean Transit Time (MTT) defined as follows:

CBV: blood volume per unit of brain matter (4-6ml/100g in gray matter)(46).

CBF: volume of blood flowing per brain mass during time interval of 1 minute (50-60ml/100g/min) in gray matter(46).

MTT: Time difference between arterial inflow and venous inflow and time peak enhancement representing time from beginning of contrast injection to maximum contrast in the region of interest(46).

These parameters are measured within a Region of Interest (ROI) and are used to detect the extent of stroke by measuring the infarcted core (decreased CBF and CBV with an increase in MTT) and surrounding penumbra (increase MTT with a moderate decrease in CBF and normal or increased CBV OR increased MTT, reduced CBF and moderately reduced CBV)(46).

The combination of using perfusion imaging and non-contrast CT could see increases in the number of patients that could be thrombolysed particularly where the time of stroke onset is unknown(43, 51)

Magnetic Resonance Imaging (MRI)

Like CT, MRI will exclude bleeds and other focal lesions(46). In early stroke, it has been found to be more sensitive and specific than CT (46). Imaging findings include loss of grey-white matter differentiation similar to CT, effacement of the surface sulci, mass effect, loss of arterial flow voids on T2 and the hyperattenuated vessel sign(46).

Images take longer to obtain than CT images making it less preferable(52).

Due the reduced availability of MRI in our setting and longer imaging times, CT remains the primary imaging modality of choice.

Time Delays

Pre-hospital delays

Despite the availability of thrombolytic therapy, low rates of thrombolysis are still found worldwide. In China in 2006 Jin *et al* found that this was due to delays in presentation to hospital. They examined presenting times in 6102 patients and found that the median time of arrival to hospital was 15 hours. Only 25% of patients arrived in the recommended 3 hour window period(53).

The factors associated with delayed presentation were presenting to the local doctor before the ED, symptom onset at home, transfer to a level 3 hospital for management and patients with a history of diabetes(53). Factors associated with early presentation were patients with haemorrhagic strokes, history of atrial fibrillation, a decreased level of consciousness, transfer by ambulance and history of coronary artery disease(53).

In a study done in Japan, less than one fifth of stroke patients presented within 2 hours. Kaneko *et al* showed that earlier presentation was associated with the severity of symptoms. Median time to hospital presentation was 12 hours(54).

In New Jersey, USA the median time of presentation to the ED was 5.7 hours with 30% of their patients presenting within 3 hours. Kothari *et al* found in this study that early presentation was associated with the use of Emergency Medical Services (EMS)(55).

In Australia, Eissa *et al* showed only 31.3% of patients arrived in less than 4.5 hours. However in this study, a significant percentage of patients(44%), had an unknown onset of presentation(56)

In London, UK Addo *et al* found only 39% presented within 3 hours with a median time of presentation of 4.73 hours(57).

In Nigeria, Phillip-Ephraim *et al* in a prospective study found that only 21% of their patients presented within 3 hours of stroke while 65.4% arrived more than 24 hours after their first symptoms. Late presentation was associated with lack of awareness of symptoms and referral from other hospitals. In this study none of the patients were brought by ambulance(58)

In Italy, 28% of patients presented within 3 hours and the average time to CT scan was 1.2 hours. The use of the Emergency Medical Services (EMS) was associated with earlier presentation(59).

It can therefore be seen that stroke patients tend to present late. More than 60% of patients in the mentioned studies presented after 3 hours (Table 2.2) - this was both in developing and developed countries.

Table 2.2 Comparison of presenting times in various regions:

USA (Kothari *et al,* 1999)	30% within 3 hours
Italy (Maestroni *et al*, 2008)	28% within 3 hours
Japan (Kaneko *et al,* 2011)	16.7% within 2 hours
China (Jin *et al,* 2012)	25% within 3 hours
UK (Addo *et al,* 2012)	39.5% within 3 hours
Australia (Eissa *et al,* 2013)	31.3% within 4.5 hours
Nigeria (Phillip-Ephrahim *et al*, 2015)	21% within 3 hours

The presumption would be that the inability of patients to perceive that they are actually having a stroke could be a significant cause for delay in presentation. However, Williams *et al* showed that even when patients knew they were having a stroke it was not necessarily associated with early presentation. Twenty five per cent of their patients could identify that they were having a stroke(60). Patients with previous strokes were more likely to recognise that they were having a stroke but even this did not lead to earlier presentation. In fact, some patients described their symptoms as “not serious”(60).

Although 55% of patients who had a stroke could describe at least one stroke symptom and 65% of patients could describe one stroke risk factor, Zerwic *et al* found that only 31.6% of these patients presented to the ED in less than 2 hours. Average time in presenting to the ED was 16 hours(9). Early presentation was found in patients with motor symptoms and the use of EMS. Very significant in this study was that someone other than the patient in 66% of cases made the choice to seek medical attention.

Because stroke can be a severely disabling disease resulting in patients being aphasic, unconscious or having motor deficits it is almost inconceivable to expect them to present within 2 hours on their own. Unfortunately, even patients that know the importance of arriving early to the ED or are aware that they are having a stroke, need to rely on someone else(9).

In-hospital delays

In-hospital delays also prolong the door-to-needle time. In this study the time to CT was collected however as this was a retrospective study the reasons for delay could not be specifically sought. The possible reasons for delay can be divided into patient factors and in-hospital factors:

Patient factors:

- An unstable patient that needs additional treatment such as glucose, blood pressure, seizure control and the need for sedation as seen by Gurav et al (10).

Hospital factors:

- Awaiting labarotory results before CT(11).
- Delays in porters transporting patients to the radiology department for CT.
- The time of CT request, perhaps after hours scanning taking longer than during normal working hours where there's more staff available(12).
- After hours may also mean a junior registrar alone looks at the CT and this may take longer than if a consultant had to interpret the scan especially in the case of subtle CT signs.
- Huang et al also found that the decision making process on whether to thrombolyse also led to delays in the door-to-needle time(11).

Summary

Successful stroke treatment require early thrombolysis inter alia(41, 42). In order to prevent permanent neurological deficits, patients should be treated as soon as possible. The current thrombolysis window is within 3 hours, and 3 to 4.5 hours for those who meet certain exclusion criteria(37). Generally, stroke patients tend to present late to the ED. Many reasons are associated with delayed and early presentation. The most common reason in various studies for delayed presentation was diabetes mellitus(53, 61, 62). Early presentation was associated with a decrease in level of consciousness and the use of EMS(53, 59). In order to meet the AHA recommendations for thrombolysis, early imaging is pivotal. The aim of imaging is to exclude contraindications for thrombolysis such as intracranial haemorrhage(43). Due to shorter imaging times and availability, CT remains the radiological imaging modality of choice(43).

For successful stroke treatment a combination of early ED presentation, early imaging and early thrombolysis is required. EMS notifying the ED before arrival and EM physician escorting the patient to CT in order to initiate treatment in the radiology department are but some factors that could reduce in-hospital delays.

3. Chapter 3 MATERIALS AND METHODS

Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Ethics Clearance certificate number is M150123-see appendix 1). Permission to perform the study at Helen Joseph Hospital was obtained from the hospital CEO (appendix 2). The collected data was kept in a password protected computer.

Study Design

Retrospective, cross-sectional, descriptive study.

Site of study

Helen Joseph Hospital ED, a tertiary hospital ED in a metropolitan area of Gauteng, South Africa. The ED sees approximately 65000 patients annually. The majority of patients have non-traumatic pathologies (approximately 70%) and the rest are trauma-related. Paediatric as well as obstetric and gynaecology patients are seen at the nearby sister-hospital, but the paediatric resuscitations and female patients presenting with ectopic pregnancies or in active labor are not uncommon.

Study Population

Inclusion Criteria:

All adult patients that presented with clinical features of a stroke to the Helen Joseph Hospital ED in the period January to December 2014.

Exclusion Criteria:

1. Trauma patients
2. Patients presenting with meningitis
3. Patient files with incomplete data or illegible documentation

Study Protocol

Data Collection

Data was collected by the researcher.

1. CT reports of patients who presented with clinical features of a stroke were found in Radiology records.
2. ED triage books were used to identify patients who presented with features of a stroke and arrival times to the ED.
3. Patient details were then used to locate files in records using patient details (Name and hospital number) and date of ED presentation.
4. Patients' demographic data, risk factors, medical history, signs and symptoms and time of stroke onset and ED presentation, time to CT were recorded on a data collection sheet. All patient data was anonymous, each patient was assigned a number instead of using names.
5. CT reports were used to record CT findings and time to CT.

This information was then captured and entered onto an electronic spread sheet (Microsoft Excel, Microsoft office for mac 2011). Data was analysed using Statistical Analysis System(SAS) version 9.4 for windows.

Data Analysis

Descriptive statistics

For continuous variables the mean and standard deviation were used to assess whether the data was normally distributed.

For continuous variables, not normally distributed, median and interquartile ranges were used.

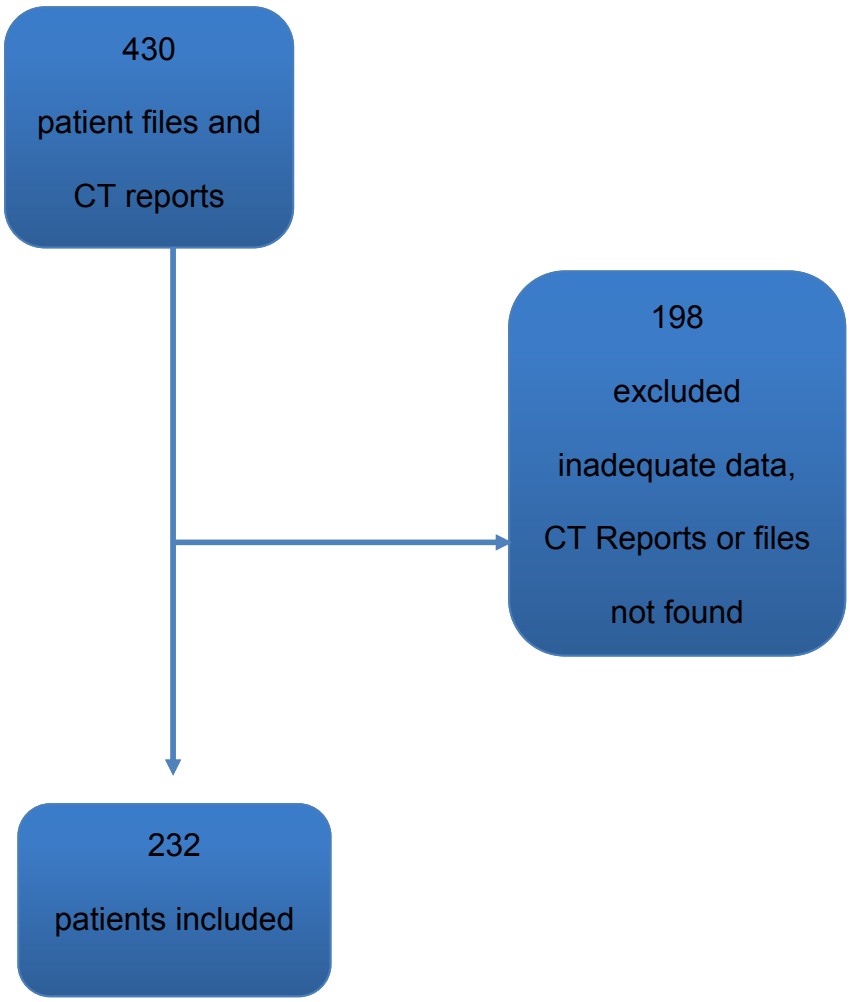
Frequencies and percentages were used to analyse categorical variables such as sex and race.

The time taken for stroke patients to present to the ED was evaluated as "time of ED arrival-time of stroke onset" and the paired t-test was used. When the exact hour of onset was not reported additional information on the files was used to approximate time of stroke onset, for example onset described as "this morning" was documented as 00:00, this afternoon 12:00, last night or woke up with symptoms time was noted as 22:00. Where the ED arrival times were noted as unknown, these patients were included in the study as the "time to CT from ED arrival" could still be calculated.

The time to CT was evaluated as "time to CT-time to ED arrival" the paired t-test was used.

The t-test was used to assess the mean for times.

Correlation and associations between risk factors and stroke was assessed. Pearson's correlation coefficient was calculated to assess the correlation. A p-value below 0.05 was considered significant.



3.1 Patient selection for ED and CT arrival time analysis

In a one year period from 1/1/2014 to 31/12/2014, a total of 430 patient files and CT reports were assessed, 198 patients were excluded due to various factors such as: file not found in patient records, CT report not found, inadequate information in the file. 232 patient's data was collected. For time to ED, 21.6% of data was missing, 182 patient data were analysed. For time to CT 0.4% of data was missing with 231 patient data analysed.

Chapter 4 RESULTS

Description of the study population

Table 4.1 below presents a description of the baseline characteristics of the patients. On average, the patients were 57 years old with a standard deviation of 15 years.

Table 4.1: Baseline Description of the study population

Characteristics	Frequency(%)
Sex	
Male	86(44.6)
Female	107(55.4)
Race	
Black	133(68.9)
White	25(12.9)
Colored	27(14)
Indian	8(4.2)

Table 4.2: Summary of medical history/habits

Characteristics	N(%) Yes	N(%) No/Unknown
Hypertension	83(43.0)	110(57.0)
Diabetes Mellitus	33(17.1)	160(82.9)
Hyperlipidaemia	18(9.3)	175(90.7)
Atrial Fibrillation	2(1.5)	191(98.5)
Previous Stroke	14(7.3)	179(92.7)
Previous Myocardial Infarction	5(2.6)	188(97.4)
HIV Positive	19(9.8)	174(90.2)
Smokers	31(16.1)	162(83.9)
Alcohol	13(6.7)	180(93.3)

Table 4.3 Summary of signs and symptoms

Characteristics	N(%)
Hemiparesis/Hemiplegia	144(74.6)
Facial Paresis	142(73.6)
Aphasia	74(38.3)
Convulsions	21(10.9)
Loss of Consciousness	31(16.1)

Table 4.4 Blood Pressure Measurements

	Frequency(%)
Elevated Blood Pressure	
Diagnosed(Known Hypertensive)	84(43.5)
Newly diagnosed(at current presentation)	45(23.3)
Normal	64(33.2)

Table 4.5 Blood glucose measurements

	Frequency(%)
Elevated Blood Glucose	
Diagnosed (Known Diabetic)	22(11.4)
Newly diagnosed(at current presentation)	14(7.2)
Normal	157(81.4)

Time to ED

Figure 4.1 Comparison of presenting times to ED

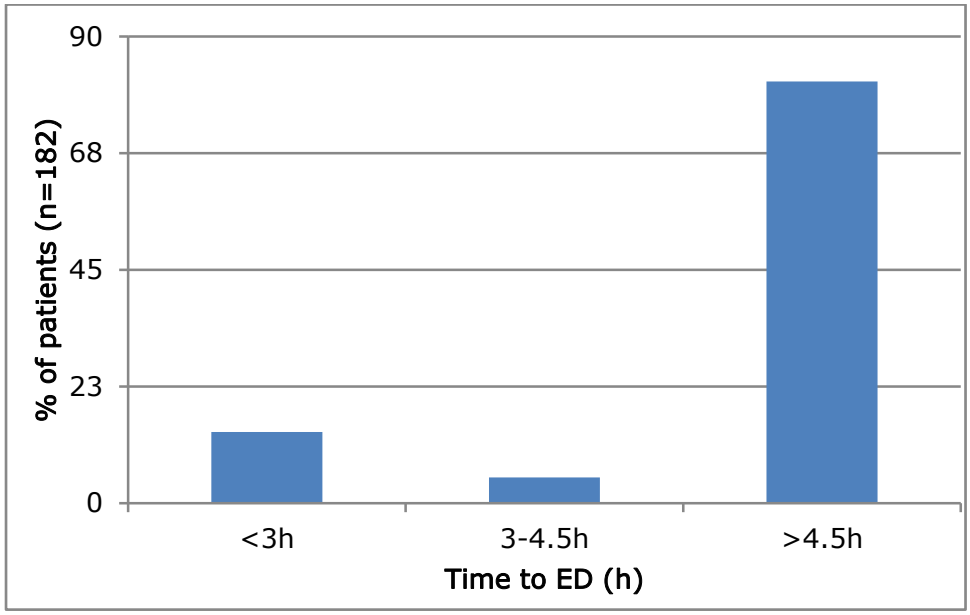
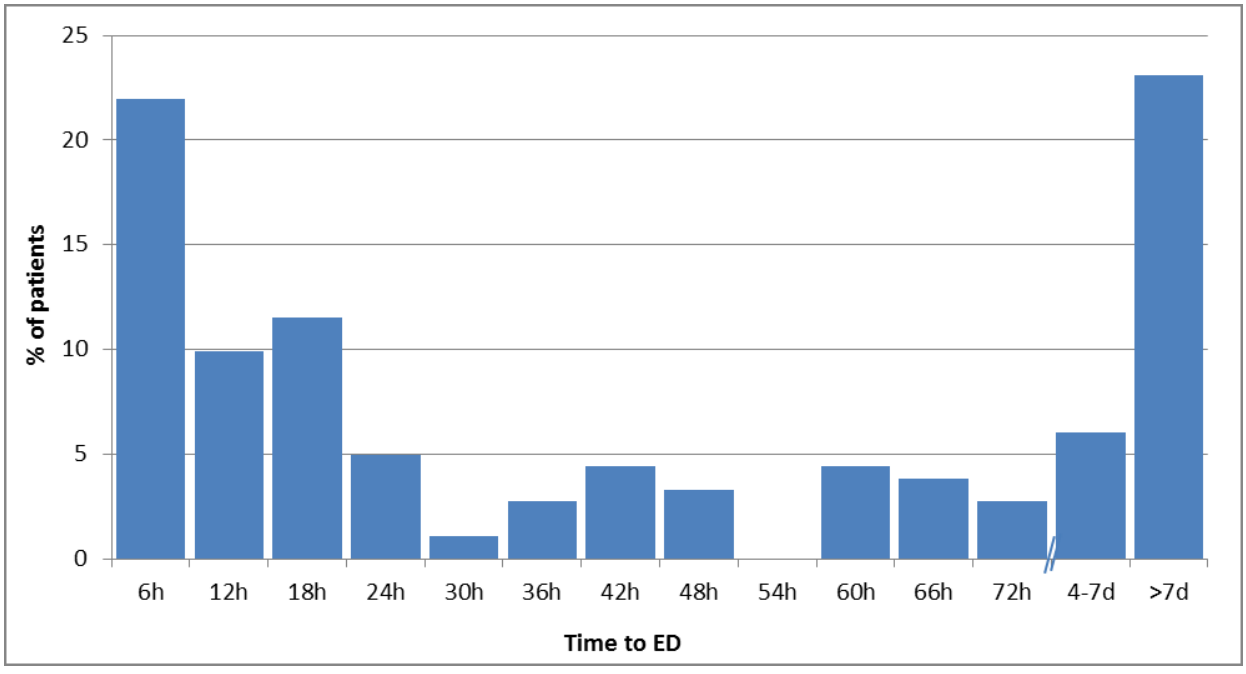


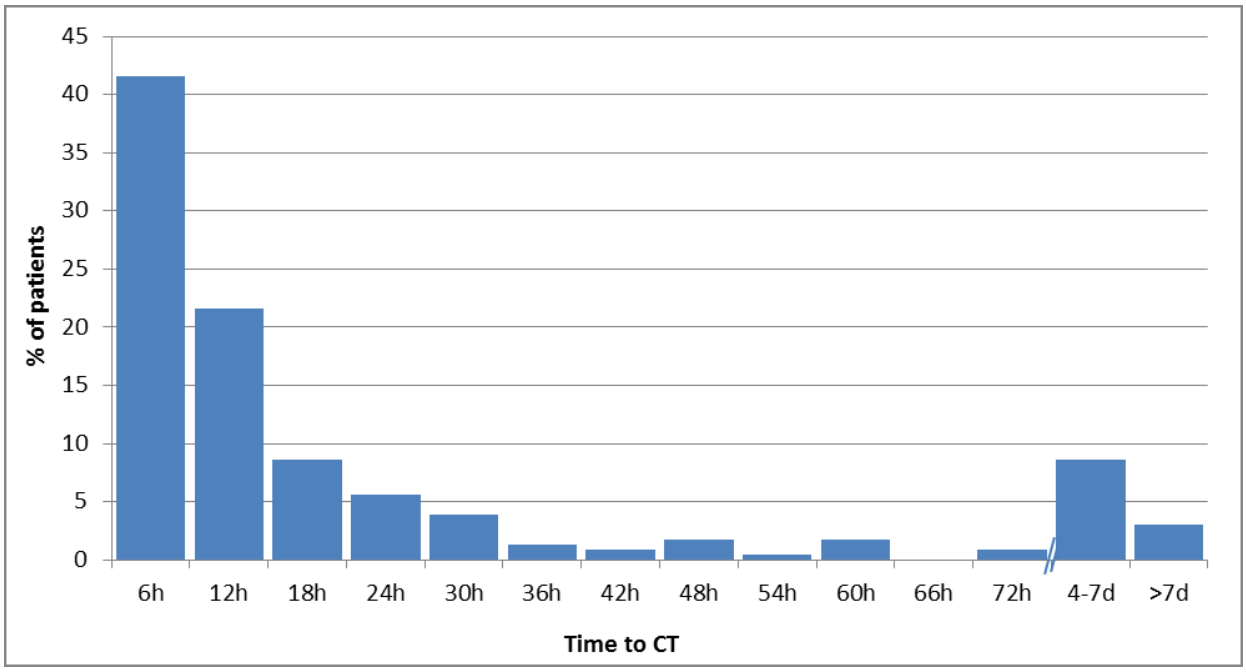
Fig 4.2 Distribution of presenting times for stroke patients to the ED



Time to ED (n=182; 21.6% missing data):

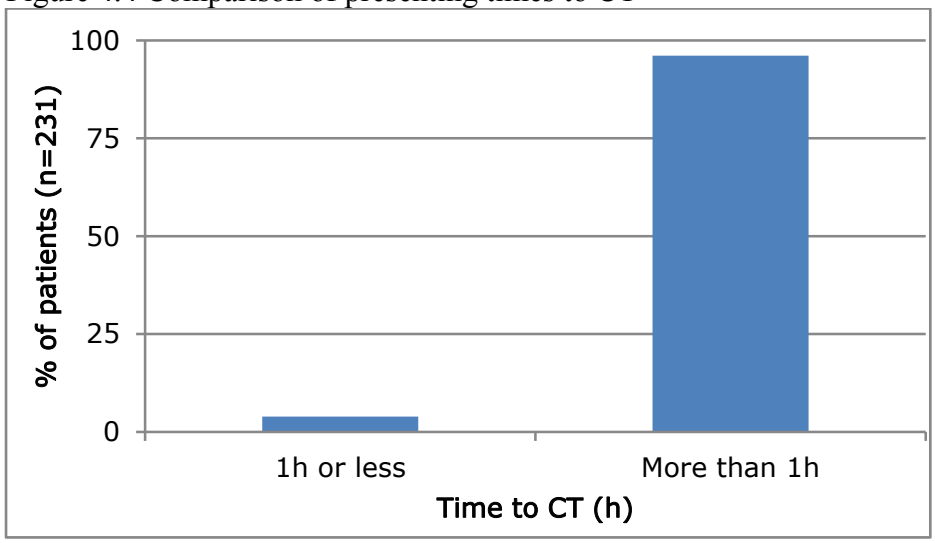
Time to CT

Fig 4.3 Distribution of presenting times for stroke patients to CT



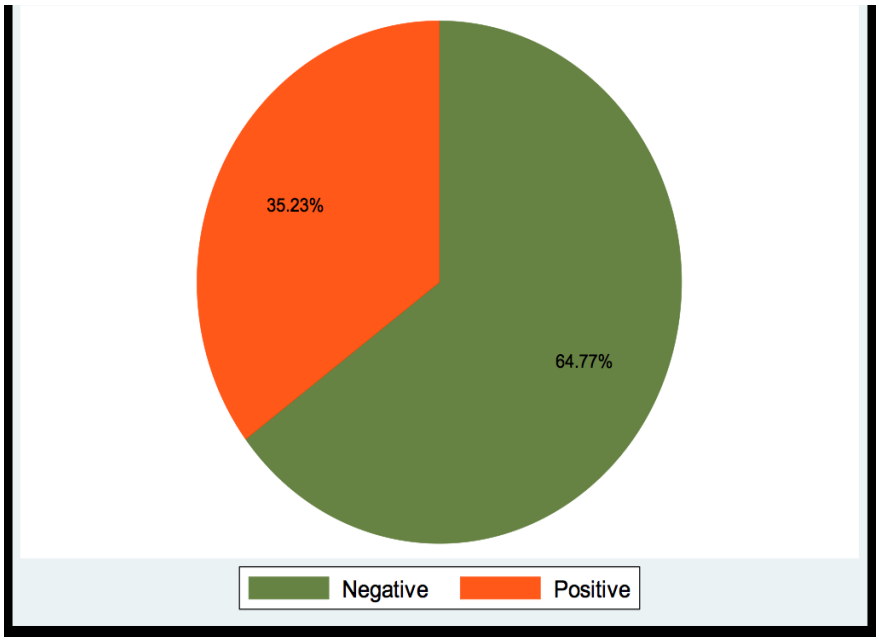
Time to CT (n=231; 0.4% missing data):

Figure 4.4 Comparison of presenting times to CT



Only 9 patients (3.9%) had a time to CT of 1 hour or less.

Figure 4.5 CT diagnosis of stroke



Of the 35.2% confirmed strokes, 75% had ischaemic strokes and 25% had haemorrhagic strokes.

Table 4.6 Other CT Findings and stroke mimics

Findings	
Normal	
Vascular	Aneurysms: Ruptured and Unruptured
	Vasculitis
Infective	Neurocystercercosis
	Cerebritis secondary to cryptococcal meningitis
	Subdural Empyema
	Fungal Sinusitis with sagittal vein thrombosis
	Rim-enhancing lesions e.g. Tuberculoma, Toxoplasmosis and cerebral abscesses.
Tumour (benign and malignant)	Meningioma
	Glioblastoma Multiforme
	Lymphoma
	Metastases
Chronic changes	Old infarcts
	Cerebral atrophy

Table 4.7: Time to Presentation by Patient characteristics

Characteristics	Time in hours		p-value
	Median	IQR	
Sex			
Male	36.25	10 – 174.2	0.12
Female	17.07	5.5 – 70.83	
Race			
Black	21.83	6.58 – 140.17	0.81
White	35.97	3.05 – 63.62	
Coloured	26.92	11.5-168.08	
Indian	46.25	3.42 – 176.65	
Smokers			
No	24.58	6.2 – 154.08	0.60
Yes	19.83	10.88 – 58.86	
Alcohol			
No	22.75	5.9 – 85.58	0.33
Yes	46	14.58 – 178.88	

Table 4.8 Time to presentation: medical history and signs and symptoms

Characteristics	Time in hours Median(IQR)		**p-value**
	Yes	No/Unknown	
Hypertension	23.2 (7-70.8)	33 (6.2-158)	0.74
Diabetes Mellitus	46.3 (14.8-189.2)	20 (5.8-84.7)	0.05*
Hyperlipidaemia	13.2 (3.3-69.8)	24.6 (7-111)	0.43
Previous Stroke	16.7 (3.4-70.8)	24.6 (6.6-85.6)	0.71
Previous myocardial infarction	4.3 (3.4-70.8)	23.5 (6.9-103.8)	0.44
HIV positive	42.6 (14-103.8)	62.9 (3.4-70.8)	0.30
Hemiparesis/Hemiplegia	33.2(8-103.8)	18.1(5.6-119.8)	0.44
Facial Paresis	33(8-103.8)	20(5.9-85.6)	0.47
Aphasia	23(5.8-132.5)	31(6.6-85.6)	0.69
Convulsions	9.8(5.3-47)	33(7-103.8)	0.22
Loss of Consciousness	6.6(2.7-21.8)	36.5(10-156)	0.001*
Elevated blood pressure	19(3-57.8)	38.5(9.8-177.8)	0.27
Elevated glucose	71.3(2.7-188.6)	23(6.7-107.4)	0.14*

Chapter 5 DISCUSSION

Basic Demographic Data

Initially 400 patient files and CT reports were collected, however due to inadequate information in the files or files that could not be located the final study sample included 232 patients. The presence of an electronic filing system and a fully functional PACS system with saved reports could have improved the sample size. The mean age of our study population was 57 year old. The majority of patients were female and black. Although the study had more females than males, the majority of patients who were eventually documented to have a stroke on CT were male. However, female patients were more likely to present earlier to the ED.

Results in context

Time to ED

The average time to presentation to the ED was 33 hours (interquartile range 8-111 hours; range 0.5-2169 hours). The majority of patients 81.3%(148) presented after 4.5 hours, with 5%(9) presenting in the 3-4.5 hour interval, and only 13.7% (25) presented within 3 hours. These are small numbers when compared to other countries. Nigeria (Phillip-Ephrahim et al)(58) and China(Jin et al)(53), 21% and 25% within 3hours respectively compared to first world countries like UK(Addo et al)(57) and Australia(Eissa et al)(56) demonstrating higher numbers presenting earlier 39.5% and 31.3% within 3 hours and 4.5 hours respectively.

Time to CT

The average time to CT was 8 hours (interquartile range 4-21 hours; range of 0.1 to 346 hours). Only 3.9%(9) had a CT scan within 1 hour, 96% had a CT after 1 hour - this is longer than the 25 minutes recommended by the AHA(30). Early CT is necessary to exclude a haemorrhagic stroke, a contraindication to thrombolysis(43). The amount of time patients spend between the ED and CT can cause significant in-hospital delays, thereby making them ineligible candidates for thrombolysis.

Lannehoa et al, found an average time to CT of 2 hours and 14 minutes in 3 EDs in France(63). Time delays were more significant in patients with an ischaemic than haemorrhagic stroke, in a study done in Nigeria by Ogbole et al(64). This was attributed to the more exaggerated symptoms that patients with haemorrhagic strokes tend to present with(64). Maestroni et al

found that patients presenting within 3 hours were more likely to have a CT earlier than patients arriving after 3 hours(59).

Patient factors influencing presentation times

The following factors were associated with earlier presentation: female, smoker and loss of consciousness - this is comparable to the study by Jin *et al*(53). Similarly, the main factor associated with delayed presentation were patients known with diabetes.

Sex

Female patients were more likely to present earlier to ED however this was not statistically significant. The average time of presentation was 17.1 hours, while male patients had a median time of presentation 36.3 hours. More males had an ischaemic stroke on CT than females. In general, there is a higher incidence of stroke in males than females(65, 66) but with increasing age, females are more likely to have a stroke than males(65, 67).

Race

There were no significant differences in presenting times amongst different races. The was a slight delay in Indian patients compared to the other race groups, however, this was not statistically significant as the sample size was smaller compared to the other races.

Smoking

Sixteen per cent (34) of patients were documented as smokers, with 83.9% as non-smokers. Smokers had a tendency to present earlier than non-smokers, with smokers presenting at a median time of 19.8 hours versus non-smokers 24.6. At 20% significance level smoking was associated with an increased incidence of stroke, 48% of smokers had a stroke on CT compared to 33% of non-smokers. This is expected as smoking is a known risk factor for stroke, with up to a 6-fold increased risk reported in smokers than in non-smokers(68). The risk increases with the number of cigarettes smoked daily(68).

Alcohol

Patients who did not imbibe alcohol presented earlier than those who did, however the reliability of this data is questionable. Patients may have been unwilling to disclose this information

accurately or may not have specifically been asked about alcohol intake. Data as to how much alcohol patients consumed per day, per week and if the patient was intoxicated at presentation for example were not collected, which also limits the results. Despite this, of the patients who admitted to using alcohol, 54% had a positive stroke on CT compared to 33.9% who did not have alcohol intake recorded. Alcohol is said to have a combined effect with hypertension, therefore increasing the risk of stroke(69). This risk is associated with intermittent peaks in systolic blood pressure associated with alcohol intake(69).

Hypertension

Hypertension is a major risk factor for stroke(70). In this study, 57% of patients were known to have hypertension. All patients' blood pressures were assessed, 33% had normal blood pressure, 67% had elevated blood pressures. On average, known hypertensive patients presented earlier than their non-hypertensive counterparts. Hypertensive patients may have a better knowledge of stroke symptoms, perhaps the reason they are more likely to present earlier than non-hypertensive patients.

Diabetes Mellitus

Seventeen per cent of patients (36) were known diabetic patients. Normal glucose levels were found in 157 patients(81.4%). Significant time delays were seen in diabetic patients (p-value: 0.05), with a median time of 46 hours, while non-diabetic patients presented within 20 hours. This is concordant with multiple studies that also showed that diabetic patients tend to present later than non-diabetics(53, 61, 62). Patients known with diabetes have also been shown to have poorer outcomes when thrombolysed for stroke(71). These include higher mortality rates, symptomatic intracranial haemorrhage and poor functional outcomes at 3 months, particularly in those diabetics presenting with elevated admission glucose levels(71). Perhaps the reason they present later is the assumption that they are hypoglycaemic or hyperglycaemic and as a result try and treat it themselves at home before coming to hospital. However, this becomes a challenge as being diabetic excludes patients from the 3-4.5 hour thrombolysis window(37). Therefore early presentation to hospital and education of stroke symptoms should be emphasised particularly to diabetic patients and their families.

Previous Stroke

Generally patients with previous stroke presented earlier with a median time of 17 hours vs 25 hours (no history of previous stroke). Despite presenting earlier, these times still do not meet the

AHA recommendations(30). Only a few presented within 3 hours, a total of 14 patients had a history of previous stroke with only 3 patients presenting within 3 hours. However, Williams *et al* showed that even when patients knew they were having a stroke, this was not necessarily associated with early presentation(60). Perhaps patients know they are having a stroke and possibly lack knowledge regarding treatment availability that could improve their outcomes?Another possibility would be that perhaps they can not arrive within the expected time due to transport unavailability. Or perhaps, as Williams *et al* found, maybe patients know that they are having a stroke but simply dismiss it as "not serious"(60).

Other(Medical history)

Hyperlipidaemia, atrial fibrillation, valvular heart disease, and previous myocardial infarction are all variables that may have also been underreported. Either not asked by the doctor taking the history or unknown by the patient's family in a case where the patient could not speak for themselves. As this was a retrospective study none of these could specifically elucidated.

Symptoms

Level of consciousness

Decreased level of consciousness was associated with earlier patient presentation to ED (p-value 0.001). The median time of presentation in unconscious patients was 6.6 hours while patients with no loss of consciousness had a median time of 36.5 hours. This was comparable to other studies where loss of consciousness was associated with earlier presentation(53, 59). Unconscious patients may be perceived as having a more serious condition than a patient with unilateral symptoms, rendering the family more likely to bring them in earlier, hence the earlier presenting time. Jin et al found a higher percentage of patients with haemorrhagic stroke presented with decreased level of consciousness compared to patients with an ischaemic stroke(53). Due to the dramatic symptoms in haemorrhagic stroke, these patients are more likely to be brought in to the ED earlier than the ischaemic stroke patients, whose symptoms may appear less severe but are more likely to benefit from early treatment.

Unilateral symptoms

The most common presenting symptoms were hemiplegia or hemiparesis and facial paresis, also known as unilateral symptoms. These are the most common and easily identifiable stroke symptoms and strong independent predictors of a stroke(8). In the current study, these factors

were not necessarily associated with early presentation in contrast to a study conducted by Gargano *et al*(13).

Thrombolysis

None of the patients in the study received thrombolysis. The biggest challenge with thrombolysis is that patients arrived at hospital after the thrombolysis window period and therefore were not eligible. Twenty-five(13.7%) patients could have potentially received thrombolysis and a further 9(5%) patients in the 4.5hour time window if they met the exclusion criteria.

Stroke Education

There is a lack of knowledge regarding stroke symptoms and the need for urgent treatment(73). As this is a retrospective study, patient knowledge was not assessed. Williams *et al* found that 75% of stroke patients could not accurately identify their symptoms as a stroke(60). Patients who had a stroke previously were more likely to identify their symptoms a stroke, but did not present to hospital early. Even patients with risk factors for stroke were not aware of symptoms and the available treatment of stroke(60). At risk patients and their families should be educated about compliance to medication, changing of lifestyle and early presentation should they develop a stroke. There is a need for stroke campaigns to improve in public knowledge. (71-75).

Stroke Mimics

The study comprised of patients who presented with symptoms of stroke. Of these, only 68 (35%) were confirmed stroke- 25% were haemorrhagic and 75% were ischaemic. These results are comparable to South African statistics for ischaemic stroke contributing 85% to all strokes and haemorrhagic 15%(18). The other CT findings ranged from normal, vascular causes, infective, benign and malignant tumours to old infarcts.

Limitations of the study

The following limited the sample size significantly:

1. Files that could not be found in records (lost files/files in pharmacy/clinic)
2. CT reports that could not be found and (Time of scan was not always documented on the report)
3. Patient times were not always documented (Time of stroke onset, time of ED arrival and time to CT)

Chapter 6 CONCLUSION

A comparison of stroke patients' presenting times show that stroke patients tend to present late in a South African context.

Certain factors were associated with early presentation. These were identified as being a female patients, smokers and those with a decreased level of consciousness. Late presentation was associated with known diabetic patients.

The average time of presentation was 33 hours which excludes patients from thrombolysis.

The average time to CT was 8 hours.

Although thrombolysis is available, none of the patients studied were thrombolysed.

According to the time to ED presentation, 25(13.7%) patients and a further 9(5%) presenting within the extended window period, could have potentially been thrombolysed.

Public education to improve awareness of early symptoms of stroke and the available treatment including the time limits could improve the management of stroke. Continuous education should be aimed particularly at the high risk patients when seen in out-patient departments for follow-up consultations.

Recommendations

Patient education including compliance with medication and knowledge of stroke symptoms and the importance of early treatment.

An electronic filing system where patient information can be accessed easier

A fully functional PACS system with CT reports stored on it.

A dedicated stroke centre with a CT scan in the ED and a stroke team

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