Access to acute stroke care: A description of stroke patients' journey to a district hospital

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Declaration

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Abbreviations

CI	Confidence interval
CT	Computed tomography
CVA	Cerebrovascular accidents
CHC	Community health centres
DALYs	Disability adjusted life years
EC	Emergency Centre
ECM	Enterprise content management (electronic medical records)
GP	General Practitioner
GSH	Groote Schuur Hospital
HECTIS	Hospital and Emergency Centre tracking information system
HIC	High-Income Country
ICD-10	International Classification of Disease, Tenth Revision
IQR	Interquartile range
LMIC	Low- and Middle-Income Country
MPH	Mitchells Plain Hospital
PACS	Picture archiving and communication system
SD	Standard deviation
TIA	Transient ischaemic attack
UCT	University of Cape Town
WHO	World Health Organization
YLD	Years lived with disability

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Access to acute stroke care: A description of stroke patients' journey to a district hospital

Abstract

Introduction

The burden of stroke in Africa has increased in the last two decades, with the population undergoing a rapid epidemiological transition, with a rise in the incidence of stroke risk factors together with the gradual aging of the population. Evidence-based guidelines for acute stroke care are often not feasible in resource challenged settings but even when resources are available, considerable delays to definitive care exists. This study aims to describe the factors that influence time from symptom onset to hospital arrival in patients that present to a district level hospital Emergency Centre with confirmed ischaemic strokes.

Methods

A descriptive analysis was performed using retrospective folder and database review. All adult patients with a confirmed ischaemic stroke presenting to Mitchells Plain Hospital Emergency Centre during the study period of 12 months (1st of January 2019 to 31st of December 2019), were eligible for inclusion. Data were collected from existing electronic patient databases and the time from onset of symptoms to hospital arrival was extracted from the clinical notes.

Results

A total of 730 (2%) patients presented with a diagnosis of stroke, of which 381 (52%) were included (CT confirmed ischaemic strokes). Only 48 (13%) presented within 4.5 hours of symptom onset and the median time from onset of symptoms to presentation to the hospital was 24 hours (IQR 12-72 hours). The majority of patients (31%) arrived via a primary public emergency medical service (EMS) call, while 29% presented directly to the hospital as self-referrals with private transport. Primary public EMS calls had the shortest call-to-hospital-arrival time (1 hour and 31 minutes), even though the median time from symptom onset to hospital arrival was still 16 hours.

Conclusion

The median time from symptom onset to hospital arrival for patients with stroke symptoms is much longer than what evidence-based guidelines suggest. The chain of survival for emergency stroke care is only as strong as its weakest link and the data from this study suggest that improvement campaigns should target stroke education and access to care.

Keywords

- Ischaemic stroke
- Prehospital
- Access to care
- South Africa
- Emergency Medicine

African relevance

- Stroke is the second leading cause of death globally
- The burden of stroke in Africa has increased in the last two decades, with the population undergoing a rapid epidemiological transition with a rise in stroke risk factors and aging population
- Evidence based guidelines for revascularisation therapy are developed in high-income countries and not always feasible in resource challenged settings
- Even when resources are available, barriers to access of care results in significant delays
- Symptom recognition, access to stroke care and barriers with healthcare seeking behaviour are challenges that disproportionately affect low-resourced settings

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Introduction

Stroke is the second leading cause of death globally, with estimates of 20 million annual stroke deaths and 70 million stroke survivors by 2030.(1,2) The burden of stroke in Africa has increased in the last two decades, with the population undergoing a rapid epidemiological transition with a rise in the incidence of stroke risk factors, together with the gradual aging of the population.(3–5) In South Africa, stroke is responsible for 25 000 deaths annually and 95 000 years lived with disability.(6) Since the year 2000 it is the third most common cause of death after HIV/AIDS and coronary artery disease.(6) Stroke is not only a leading cause of death but also results in long term disability and is associated with significant economic losses.(7) It is estimated that between 3-4% of the total health care expenditure in high-income countries (HICs) is spent on stroke care, with the mean lifetime cost of ischaemic stroke per person estimated at $140 048 in the United States.(8) There is a paucity of data describing the economic burden of stroke care in Low- and Middle-Income Countries (LMICs). A study in rural South Africa demonstrated a loss of disability adjusted life years (DALYs) of 1 552 per 100 000 person years due to stroke, twice as high as estimates for high-income countries during the same time period with the estimated costs of stroke care being between 1.6-3% of the total health expenditure.(1,8,9) The costs of stroke reach far beyond those incurred by health services, with informal care and productivity loss both contributing greatly to the overall financial burden.(10)

Several evidence-based guidelines provide recommendations for acute stroke care. A focus on the role of emergency medical services early recognition and transport to dedicated stroke units, early imaging and neurologist review, and early intervention through lysis and/or endovascular treatment.(11,12) Rapid assessment and stabilisation by EMS with transport to dedicated stroke units and stroke education to health care personnel, dispatchers, EMS personnel and the general public have demonstrated improved outcomes significantly.(13,14) The use of intravenous thrombolysis for acute ischaemic stroke is controversial, but the benefits of early revascularisation and early admission to a dedicated stroke units has been shown to decrease mortality as well as costs.(15–17) These guidelines are however developed in High-Income Countries (HICs) and are not appropriate for resource challenged LMICs, where the severely ill and injured are still unable to access good quality prehospital and acute care.(18–20) Chunga et al. (2019) demonstrated that prehospital services and national emergency numbers were lacking in LMICs, along with significantly less access to specialist neurology and radiology services.(20)

Even when resources are available for reperfusion therapy, most patients in LMICs remain ineligible, due to delays in seeking help after symptom onset, or a lack of access to acute stroke care.(21) Intravenous thrombolysis can be considered for patients who presents within 4.5 hours of onset of symptoms, with specific considerations for those who awoke with stroke symptoms, and endovascular thrombectomies can be performed up to 24 hours post onset of symptoms in selected patients.(11,12,22) A paucity of data that explores the barriers of access to acute stroke care in LMICs, however, impedes the development of locally applicable guidelines. This study aimed to describe the factors that influence time from symptom onset to hospital arrival in patients that present to a district level hospital Emergency Centre (EC) with confirmed ischaemic strokes.

Methods

Study design

A descriptive analysis was performed, using a retrospective folder and database review as data collection method.

Setting and population

The study was conducted at Mitchells Plain hospital (MPH), a district level hospital in the Mitchells Plain Health District of the Metro Region, which is approximately 32km from Cape Town's city centre. The hospital serves a low- to middle-income population of approximately 600 000, which includes the population of Mitchells Plain and the greater part of Philippi, a low-income community in a large nearby township. Mitchells Plain EC attends to an average of 4 000 patients per month with a high burden of non-communicable diseases as well as HIV/TB and trauma. Mitchells Plain Hospital does not have an onsite stroke centre, or neurology services and only have access to Computed Tomography (CT) scans during office hours (08:00-16:00). Patients with confirmed or suspected ischaemic strokes who are eligible for revascularisation therapy are promptly transferred to a tertiary hospital 22 km away.

Sampling

All adult patients with a confirmed ischaemic stroke presenting to Mitchells Plain Hospital EC during the study period of 12 months (1st of January 2019 to 31st of December 2019), were eligible for inclusion. Data from consecutive adult patients (>18 years old) with confirmed ischaemic strokes as confirmed on CT of the brain, were collected. Patients with stroke mimics, those who did not have a CT brain, those transferred from private ECs with missing data and patients who developed ischaemic strokes as an inpatient, were excluded.

Data collection procedures

Data were collected in four stages. During the first stage, the electronic registry Hospital and Emergency Centre Tracking and Information system (HECTIS) was searched for patients with a clinical diagnosis of a stroke using the International Classification of Diseases 10th revision (ICD-10) codes. HECTIS is an official provincial application used across the Western Cape to help track patients' throughput in the EC. Stage two assessed the Picture Archiving and Communication system (PACS) for patients identified in stage one for their CT Brain scan reports. PACS is the official provincial digital application where radiological images can be reviewed, and reports accessed. Confirmation of ischaemic stroke was sought through the presence of signs of an ischaemic stroke or the absence of alternate pathology in an otherwise normal scan. Stage three entailed a manual extraction of information from the clinical notes stored on the Enterprise Content Management (ECM) registry. ECM is an official provincial application used for electronic storage of clinical notes and other documentation. During the final stage, the ETriage database was utilised to obtain information for patients who were transported via EMS. Etriage is an official electronic database used by the Western Cape EMS to document clinical assessment and transfer details and with process times. Data were collected by the study investigators. Folder numbers were used to track patients through phases and patients were deidentified as soon as the data collection process was completed. Cases were excluded if patients' clinical data or information were missing or inaccessible. Incomplete data were included and described up to the point where it could no longer be analysed, and demographics were presented for both missing and incomplete data. The time from symptom onset to hospital arrival was obtained from all clinical notes via ECM. If the specific time of onset was not documented or unclear, the closest possible time category, as adopted from Khalema et al. (2018) was used, with up-rounding of estimates.(18) Evidence recommends thrombolysis within 3 hours of onset of symptoms, with an extension to 4.5 hours in certain patient groups.(12) Mechanical thrombectomy is recommended up to 16 hours, but can be extended to 24 hours in eligible patients, hence the addition of further categories.(12)

Data analysis

A convenience sample size of approximately 350 over the 12 month data-collection period was anticipated based on the findings of Mayet et al. (2021).(23) Descriptive statistics were used to describe demographics and categorical variables were described and tabulated as proportions and percentages. Categorical variables were analysed for non-random associations by using the Chi^2 test, and continuous variables with the help of the Mann-Whitney U test. Statistical significance was defined as a $p<0.05$. Microsoft Excel was used to manage data initially and SPSS Version 28 was used to perform the analysis.

Ethical considerations

No identifying data were collected. Initially, patients' folder numbers were used to extract relevant data from the various databases and registries. A unique study number was assigned to each patient and corresponding folder numbers were saved in a separate file in case of a query. Ethical approval was obtained from the University of Cape Town's Health Research Ethics Committee (HREC 610/2020) and facility approval through the National Health Research Database website (WC_202010_023).

Results

A total of 49 577 patients presented to the EC during the one-year study period of which 38 126 (77%) were adults. Of the 730 (2%) identified with a clinical diagnosis of a stroke, 381 (52%) were included in the final sample. Figure 1 details the exclusions.

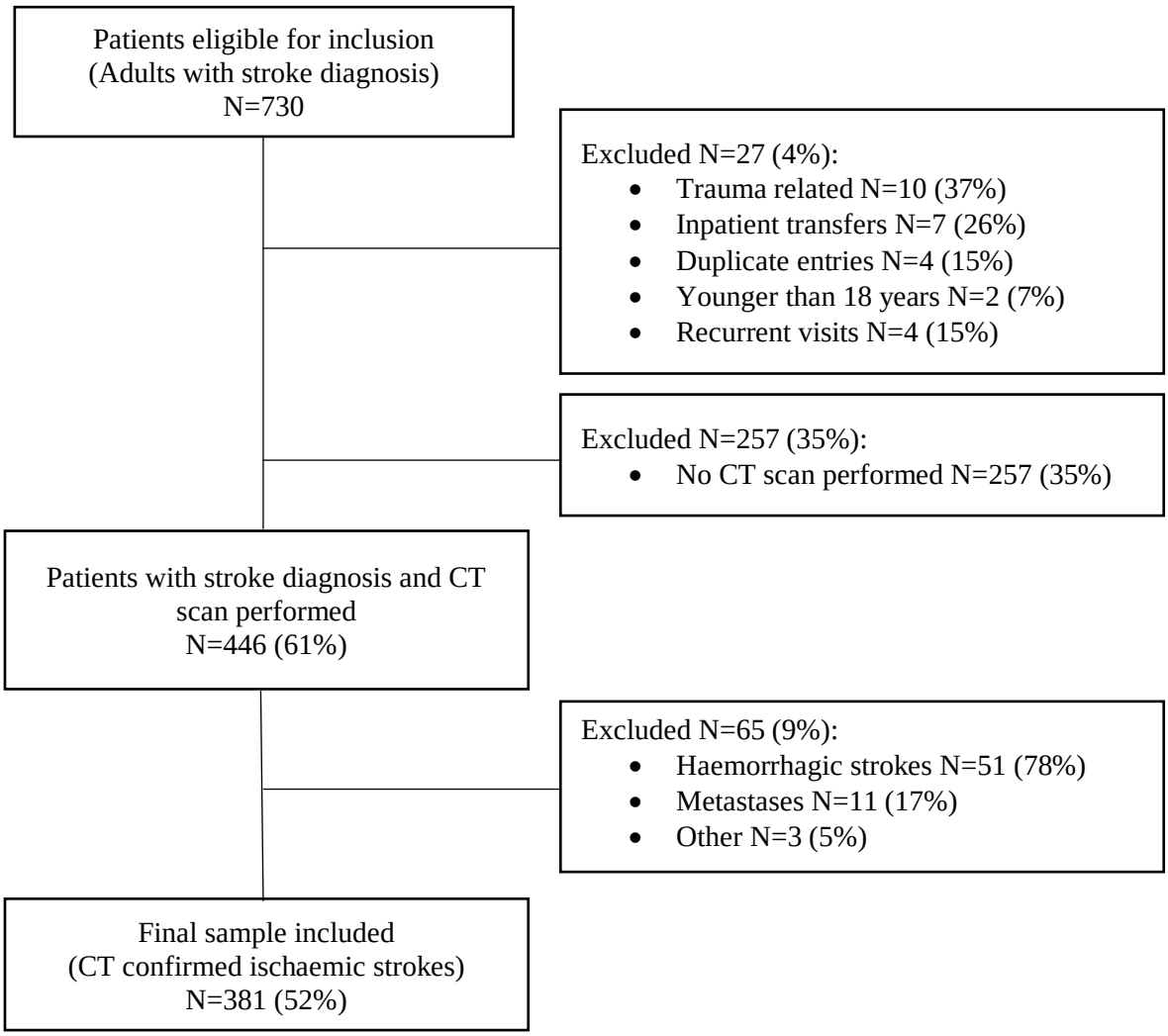

Figure 1: Flow diagram of study participants

Of the 381 patients, 195 (51%) were females and 186 (49%) males. The age distribution was skewed to the left around a median of 62 years, with the youngest and oldest participant being 21 and 90 years old respectively. The majority of patients were in the >65 years old category (n=141, 37%), and 53 (14%)

of patients were under 45 years old (young stroke). Most patients were either unemployed (n=101, 27%) or earning less than R8 333 per month per family unit (n=268, 70%). A total of 48 (13%) patients presented within 4.5 hours of symptom onset and the median time from onset of symptoms to presentation to the hospital, was 24 hours. The majority of patients arrived via a primary public EMS call (n=119, 31%) while 112 (29%) patients presenting directly to the hospital as self-referrals with private transport. Of the patients who arrived via a primary public EMS call, 27 (23%) presented within 4.5 hours of onset of symptoms, with a median time of 18 hours from symptom onset to hospital arrival. Even though only a small subset of patients, patients within the highest income category had the shortest delay from symptom onset to hospital arrival (12 hours) and had the biggest proportion (60%) arriving within 12 hours from the onset of symptoms, with 80% using private transport. Table 1 depicts demographical and clinical characteristics of all patients for each presenting time category. In total, 160 (42%) patients had the time of onset documented clearly, with a specific time documented. A total of 197 (52%) were documented as days and/or weeks e.g., symptoms started 2 days ago. In this instance the time frame was categorised to the closest applicable. For 24 (6%) patients the time of onset of symptoms was not documented in any of the medical notes.

Table 1: Demographical and clinical details of all patients per presenting time category (n=357)

N (proportion)	Total	<3 hours	<4.5 hours	<12 hours	Symptom onset to hospital arrival (hours) Median (IQR)	Missing data*
Overall	381	36 (10%)	48 (13%)	128 (36%)	24 (12-72)	24
Age categories						
18-25	2	1 (50%)	1 (50%)	1 (50%)	13.5 (3-24)	0
26-35	16	1 (6%)	1 (6%)	3 (19%)	36 (16-96)	2
36-45	35	4 (11%)	4 (11%)	11 (31%)	24 (12-48)	2
46-55	81	6 (8%)	7 (9%)	21 (26%)	25 (14-96)	4
56-65	106	8 (8%)	10 (10%)	35 (33%)	24 (12-72)	6
>65	141	16 (12%)	25 (18%)	57 (40%)	23 (8-48)	10
Gender						
Male	186	14 (8%)	19 (10%)	62 (33%)	24 (12-72)	8
Female	195	22 (12%)	29 (15%)	66 (34%)	24 (11-72)	16
Income category**						
Unemployed	101	12 (12%)	14 (14%)	43 (43%)	18 (9-72)	6
< R8 333 per month	268	22 (8%)	32 (12%)	80 (30%)	24 (12-72)	18
R8 333 ≤ R29 166 per month	7	1 (14%)	1 (14%)	2 (29%)	72 (9-168)	0
> R29 16 per month	5	1 (20%)	1 (20%)	3 (60%)	12 (6-24)	0
Type of presentation						
Clinic referral	71	1 (1%)	1 (1%)	24 (34%)	17 (11-48)	1
Self-referral	112	13 (12%)	16 (14%)	39 (35%)	24 (12-72)	10
Primary EMS	119	18 (15%)	27 (23%)	50 (42%)	18 (6.5-48)	7
GP referral	76	4 (6%)	4 (6%)	15 (20%)	48 (18-120)	6
Other	3	0 (0%)	0 (0%)	0 (0%)	80 (48-96)	0
Mode of transport						
Public EMS	183	19 (11%)	28 (16%)	73 (40%)	17 (8.5-48)	7
Private	197	17 (9%)	20 (10%)	55 (28%)	24 (12-96)	17
Private EMS	1	0 (0%)	0 (0%)	0 (0%)	96 (96-96)	0
Day of the week						
Monday	57	10 (18%)	10 (18%)	23 (40%)	24 (12-48)	3
Tuesday	63	6 (10%)	7 (11%)	16 (25%)	24 (12-48)	6

Wednesday	61	3 (5%)	6 (10%)	24 (39%)	24 (12-72)	1
Thursday	60	7 (12%)	9 (16%)	20 (33%)	24 (11-75)	7
Friday	63	3 (5%)	5 (8%)	17 (27%)	24 (12-96)	2
Saturday	38	3 (8%)	6 (16%)	12 (32%)	18 (11-72)	3
Sunday	39	4 (10%)	5 (13%)	16 (41%)	14 (7-25)	2
Weekend						
Yes	77	7 (9%)	11 (15%)	28 (36%)	17 (9-48)	5
No	304	29 (10%)	37 (12%)	100 (33%)	24 (12-72)	19
***Office hours						
Yes	153	13 (9%)	16 (11%)	45 (29%)	25 (12-72)	10
No	228	23 (10%)	32 (14%)	83 (36%)	24 (10-48)	14
EC Disposition						
Discharged	80	4 (5%)	5 (6%)	22 (28%)	48 (12-96)	2
Admitted	293	29 (10%)	40 (14%)	103 (35%)	24 (11-48)	20
Transfer up	5	3 (75%)	3 (75%)	3 (60%)	25 (1-62)	1
Deceased in the EC	1	0 (0%)	0 (0%)	0 (0%)		1
Other	2	0 (0%)	0 (0%)	0 (0%)	20 (16-24)	0
Stroke location						
Home	370	33 (9%)	45 (12%)	124 (34%)	24 (12-72)	24
Recreational	3	1 (33%)	1 (33%)	1 (33%)	24 (2-48)	0
Work	4	1 (25%)	1 (25%)	2 (50%)	87 (4-168)	0
Other	3	1 (100%)	1 (100%)	1 (100%)	75 (48-80)	0
Awoke with stroke						
Yes	50	0 (0%)	1 (2%)	21 (42%)	21 (12-24)	0
No	325	36 (11%)	47 (15%)	107 (33%)	24 (10-72)	18

*24 cases with missing data not included in calculations **Income per family unit ***Office hours 08:00-16:00
EMS Emergency Medical Services, GP General practitioner, EC Emergency Centre

Time from symptom onset to hospital arrival did not differ significantly during weekdays, with a median of 24 hours across the days of the week. On weekends, the median reduced to 18 and 14 hours on Saturday and Sunday respectively. More patients arrived within 12 hours of onset of symptoms outside of office hours (29% vs 36%), even though the median time from symptom onset to hospital arrival were similar (25 vs 24 hours). A large proportion of patients (n=293, 77%) were admitted and almost all of the patients, 370 (97%), developed symptoms at home. Patients who required admission presented sooner than those who were discharged from the EC (median: 24 hours vs 48 hours after onset of symptoms), as well as those who woke with symptoms of a stroke (median: 21 hours vs 24 hours).

Figure 2 categorises the time from symptom onset to hospital arrival with more than 60% of patients arriving after 12 hours of symptoms onset, and more than 30% arriving after 24 hours of symptom onset. Nearly 5% of patients presented after more than a week of symptoms.

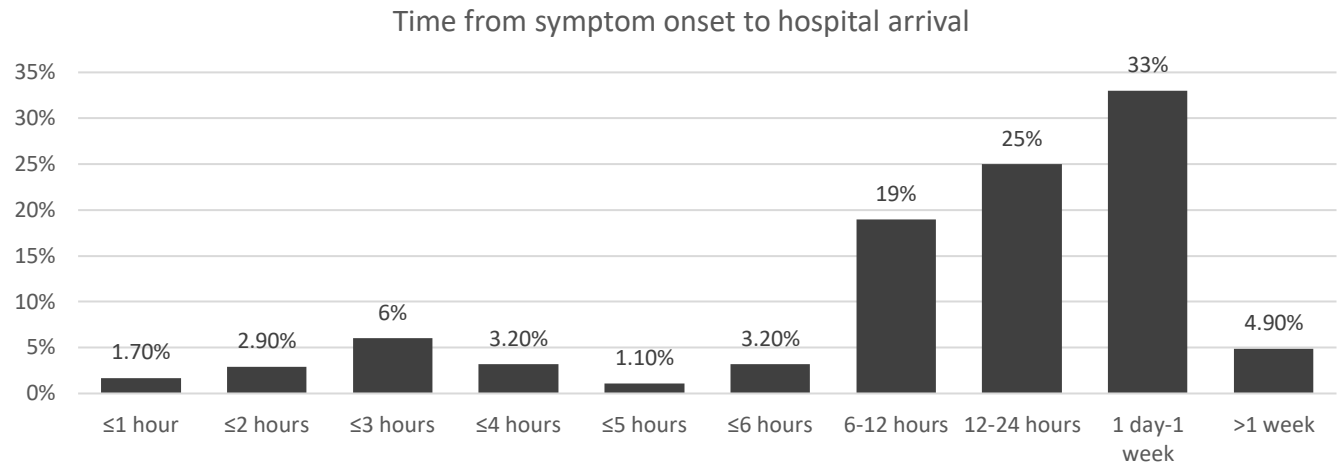

Figure 2: Proportional breakdown of time from symptom onset to hospital arrival (median)

Figure 3 represents the timeline from symptom onset to hospital arrival for each type of presentation. Patients either presented directly or via the GP with their own private transport, or with EMS directly from scene or via the clinic. The shortest time from symptom onset to hospital arrival occurred with clinic referrals that were transported by public EMS (16 hours), with a mean EMS call-to-hospital-arrival time of 2 hours and 27 minutes. Primary public EMS calls had the shortest call-to-hospital-arrival time (1 hour and 31 minutes), even though the median time from symptom onset to hospital arrival was still 16 hours.

Type of presentation	Mode of transport (hours: minutes)	Symptom onset to hospital arrival (hours)
GP referral (20%)	Private transport	48 (18-120)
Primary EMS (31%)	Call to hospital arrival: 1:31 (1:03-2:40)	18 (6.5-48)
Self-referral (29%)	Private transport	24 (12-72)
Clinic referral (19%)	Private transport (13%)	132 (48-168)
	EMS (87%); Call to hospital arrival: 2:27 (1:04-4:37)	16 (10-48)

Figure 3: Breakdown of timeline of symptom onset to hospital arrival (median(IQR))

Table 2 provides a breakdown of the time from symptom onset to hospital arrival for patients who arrived via primary public EMS calls. Of the 119 patients that arrived via primary public EMS calls, 101 (85%) had a documented EMS presentation on the EMS electronic records. A total of 81 (80%) EMS presentations correlated with a stroke or stroke like symptoms including, *CVA/Stroke* (44%), *TIA* (4%), and *unilateral weakness* (32%). When grouped together, no significant difference was noted when compared to the rest of the documented presentations (scene time p=0.118, EMS call to arrival on scene p=0.099 and EMS call to hospital arrival p=0.376). The median time from symptom onset to hospital arrival, however, was associated with a significant shortening in those with documented EMS presentations of stroke (18 vs 24 hours, p=0.005). The overall time from symptom onset to hospital arrival is similar to those who presented via the clinic, (17 vs 17 hours) but shorter than the self-referrals (17 vs 24 hours).

Table 2: Documented EMS presentations and breakdown of time from symptom onset to hospital arrival (median (IQR)* (n=363)

	Total (column%)	EMS call to arrival on scene (hours:minutes)	Scene time (hours:minutes)	EMS call to hospital arrival (hours:minutes)	Symptom onset to hospital arrival (hours)
Overall	101	0:50 (0:21-1:52)	0:18 (0:12-0:25)	1:33 (1:03-2:41)	17 (6-25)
Collapse / syncope	4 (4%)	1:17 (0:48-6:47)	0:16 (0:07-0:38)	2:19 (1:20-8:12)	14 (8-32)
Hyperglycaemia/DKA	3 (3%)	0:57 (0:50-2:55)	0:18 (0:16-0:20)	1:53 (1:29-3:25)	24 (4-72)
Unresponsive	5 (5%)	0:41 (0:40-0:46)	0:16 (0:11-0:28)	1:26 (1:23-1:48)	18 (8-30)
CVA / Stroke	45 (44%)	1:02 (0:20-2:17)	0:18 (0:10-0:23)	1:37 (0:59-3:13)	24 (10-48)
Weakness / Body weakness	4 (4%)	1:02 (0:12-4:30)	0:22 (0:16-0:41)	2:05 (0:50-5:29)	24 (18-24)
TIA	4 (4%)	2:17 (0:43-4:03)	0:16 (0:07-0:24)	2:47 (1:40-4:48)	31 (11-48)
Dizziness	1 (1%)	1:23 (1:23-1:23)	0:25 (0:25-0:25)	1:59 (1:59-1:59)	4 (4-4)
Body pain / Stiff body	2 (2%)	1:02 (0:29- 1:36)	0:31 (0:26-0:36)	1:49 (1:11-2:27)	169 (3-336)
Unilateral weakness	32 (32%)	0:36 (0:18-1:27)	0:17 (0:12-0:25)	1:19 (0:56-2:19)	12 (4-24)
Other	1 (1%)	0:17 (0:17-0:17)	0:21 (0:21-0:21)	1:00 (1:00-1:00)	4 (4-4)

* 18 patients excluded with missing and/or incomplete EMS data

Discussion

The stroke burden of 2% of all patients that presented to the EC is significant, considering the long-term disability and economic impact a stroke has on the individual, family structures and the community at large. This is much higher than reported previously in other provinces of South Africa (0.47 and 0.39 per annum), but similar to a previous study in the Western Cape.(18,23,24) The proportion of ischaemic and haemorrhagic stroke was in keeping with local data and what is reported in the United States of America and Europe (85% and 11% respectively) but in contrast to data from other LMICs where the proportion of haemorrhagic stroke is reported as much higher ranging from 29-57%.(6,10,23,25,26) The median age of 60 years, is congruent with local stroke data, but much lower than the median age of 73 in high-income countries.(18,23,26–29)

The overall time to hospital arrival following onset of symptoms suggestive of a stroke was much longer (median of 24 hours) as compared to high-income countries where it has been reported to be between 3-6 hours.(4) Very few patients (13%) presented within 4.5 hours of symptom onset. A recent study from South Africa reported the median time from symptom onset to hospital arrival to be 33 hours (IQR 8-111), with 19% of patients arriving within 4.5 hours of symptom onset.(18) These findings are comparable to the findings from our study, perhaps suggesting generalisability of the data to the public health setting in South Africa.(29)

Factors that were associated with earlier presentation included age >65 years (18%), female gender (15%), patients admitted to hospital (14%) and patients arriving with public EMS (23%). Studies from Asia demonstrated that patients >65 years old presented sooner, with the postulation that they are more aware of stroke symptoms, hence the earlier presentation.(27,29) In contrast, data from HICs demonstrated no impact of age on time to hospital arrival in patients with acute ischaemic strokes.(30,31) Factors associated with a delay in presentation included younger patients, under 45 years, (11%), those arriving via GP (6%) and the clinic (1%) and those who awoke with a stroke (2%). This was also demonstrated in numerous international studies where referrals from other medical facilities as well as awakening with symptoms lead to longer delays to hospital presentation.(27,31,32) Patients who arrived at the hospital via primary EMS calls had the shortest delays from symptom onset to hospital arrival, congruent with international data.(4,13,14,28) Considering the relatively quick median EMS call-to-hospital-arrival time of 1 hour and 31 minutes, it is evident that the longest delays occurred before EMS was activated. This could either signify a lack of symptom recognition or a delay in the decision to access health care. Time from symptom onset to hospital arrival was much shorter for patients who presented during the weekend. This is in contrast to other studies in high income countries where time of symptom onset and weekday presentation are associated with shorter delays.(28,32,33)

Anecdotally, this could be due to better access to transport or improved stroke symptom recognition with the rest of the family or support structure at home, rather than at work. Our study also demonstrated shorter symptom onset-to-hospital-arrival times in patients in the highest income category, where 80% using private transport. Patients who required admission presented sooner than those who were discharged, probably because they had more severe symptoms and it was more obvious or apparent.

A total of 31% patients arrived with EMS of which 65% were via primary EMS calls. Even though there is a paucity of evidence evaluating EMS utilisation as primary access to acute stroke care in Africa, two studies reported very low rates (0% and 7% respectively).(18,34) LMICs often have ineffective or immature prehospital services as well as a lack of a national emergency number, potentially contributing to a lower EMS utilisation rate.(20) The proportion of patients with symptoms of a stroke that are transported to hospital with EMS in high-income countries, however, are reported to be as high as 60%.(29) The median EMS call-to-hospital-arrival time in our study was 1 hour and 31 minutes, as opposed to 44 minutes reported in North West of England.(35) Patients transferred by EMS from surrounding clinics had a longer time to hospital arrival with a median call-to-hospital-arrival time of 2 hours and 27 minutes. In the United States, scene time for EMS for stroke patients ranges from 13-20 minutes, with guidelines recommending a scene time of 15 minutes for 90% of calls for suspected stroke cases.(36) Our study found the median scene time for all calls to be 18 minutes and when stroke symptoms correlated with EMS presentations, 17 minutes. A study in the United States found EMS sensitivity for stroke recognition to be 74%, with a meta-analysis of the Cincinnati Prehospital Stroke Scale demonstrating sensitivities ranging from 79-95%.(37) We found that of the 101 patients in whom a presentation was documented, 81% correlated with a stroke or stroke-like symptoms. This is in keeping with findings from a study in the United States, where only after implementation of a stroke educational programme, EMS stroke recognition improved from 61% to 79%.(13) Commonality was found in the missed cases, with generalised weakness and dizziness also described in other international studies.(37)

This is the first study of its kind in the Western Cape that describes how patients with a stroke access health care and the delays that are associated with various prehospital factors. The information gained from this study will help understand the barriers to timeous access to stroke care and help inform future research and health policies. This study however only described data from a single centre and inferences may therefore not be generalisable. However, the results do mimic the only other study like this from South Africa.(18) Extracting the exact time from onset of symptoms to hospital arrival is not always possible or accurate with retrospective data and a prospective approach could present more accurate data. Another limitation is the fact that disease severity as a confounder was not investigated and the

affect is therefore not known. This many have impacted time from symptom onset to arrival, as well as mode of transport. Future studies should investigate different geographical areas and consider a prospective data collection method. A prospective regional stroke-registry could provide valuable answers and should be considered.

Conclusion

Even though EMS response times were reasonably swift and comparable to high-income settings, long delays prior to activating EMS resulted in very long symptom onset-to-hospital-arrival times. This may suggest significant barriers with symptom recognition, accessing stroke care or with (a lack of) healthcare seeking behaviour, and should be qualitatively explored. The chain of survival for emergency stroke care is only as strong as its weakest link and the data from this study suggest that improvement campaigns should be focused on the delays prior to accessing health services, including stroke education and access to care.

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Dissemination of Results

The findings of this study have been disseminated to the Emergency Centre and Hospital managers, as well as to the Faculty of Emergency Medicine Cape Town.

Authors' Contributions

Authors contributed as follow to the conception or design of the work (CH, UG and ROM); the acquisition (CH and ROM), analysis (CH), or interpretation (CH, UG, and ROM) of data for the work; and drafting the work (ROM) or revising it critically for important intellectual content (CH, UG, and ROM): ROM contributed 50%; CH 40%; and UG 10%. All authors approved the manuscript to be published and agreed to be accountable for all aspects of the work.

Declaration of Competing Interests

CH is an associate editor of the African Journal of Emergency Medicine. CH was not involved in the editorial workflow for this manuscript. The African Journal of Emergency Medicine applies a double blinded process for all manuscript peer reviews. The authors declared no further conflicts of interest.

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Part B: Addenda

Addendum 1: Acknowledgements

The authors acknowledge the HECTIS team, especially Dr Parak and Mr Jacques De Villiers for the integrity of the data.

Addendum 2: Author Guidelines (African Journal of Emergency Medicine)

https://www.elsevier.com/journals/african-journal-of-emergency-medicine/2211-419X/guide-for-authors

Addendum 3: Research Proposal

Dissertation Proposal

Access to acute stroke care: A description of factors that influence time from symptom onset to hospital arrival

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This study is in partial fulfilment of the Master of Medicine (Emergency Medicine) degree

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Declaration

I, Dr Ryan O'Meara, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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_____

Ryan O'Meara

List of abbreviations

ADL	Activities of Daily Living
CT	Computed Tomography
CNS	Central Nervous System
CVA	Cerebrovascular Accident
DALYs	Disability Adjusted Life Years
EC	Emergency Centre
ECM	Enterprise Content Management
EMS	Emergency Medical Services
ICD-10	International Classification of Diseases 10th Revision
ICH	Intracerebral Haemorrhage
LMIC	Low – to middle - income
PACS	Picture Archiving and Communication System
SAH	Subarachnoid Haemorrhage

Abstract

Introduction

Cerebral vascular accidents (CVA's) are a major burden on society causing significant morbidity and mortality. Early recognition and presentation to a hospital allows for potential intervention with the aim to reduce morbidity and mortality, thus decreasing the burden on the health care systems and family. Even though district hospitals in the Western Cape do not have dedicated stroke units, they do have the ability to facilitate care at a higher level. Detailed information on how patients with acute strokes access care could inform prehospital practice, future resource allocation and clinical guidelines.

Methodology

This study will be a descriptive analysis, assessing patients with ischaemic strokes presenting to a district level hospital. Eligible patients will be identified from the HECTIS (Existing) ICD-10 database where and only patients with computed tomography (CT) confirmed ischaemic strokes will be eligible for inclusion. EMS details will be extracted manually from the ETriage database. Data will be collected for 12 months and an expected sample of 350 cases are expected.

Ethical Considerations

Data will be deidentified as soon as the data collection process is completed. Only the folder number will be used to track patient details between databases. Data collection will follow a retrospective folder review and will only collect existing data. Considering the low ethical risk to patient confidentiality, a waiver of consent will be applied for. No data regarding treating clinician or facility will be recorded and there is no risk to the community or hospital. Ethical approval will be sought through University of Cape Town (UCT), Human Research Ethics Committee (HREC) and National Health Research Database (NHRD) approval will follow.

Conclusions

This study will describe the factors that affect prehospital delays for patients who present with an ischaemic stroke. The information gained may be used to inform future guidelines and policies around prehospital stroke care. A publication in a peer reviewed journal is anticipated

Introduction

Background

Stroke is traditionally defined as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS), which occurs on a vascular basis. Stroke subtypes include ischaemic stroke/cerebral infarction, intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) .(1)

The Global Burden of Disease study 2010, found that stroke is the second leading cause of death internationally. It also reported stroke as the third most common cause of disability adjusted life years (DALYs). The incidence of stroke was higher in low-middle income countries, and contributed significantly to the burden of disease.(2) In 2016 cerebrovascular disease accounted for 5.1% of natural deaths, sitting in the top 5 for causes of natural deaths for the year.(3)

The effects of stroke are far reaching. Acutely, neurological deficits which are likely to persist causes impairment in the social, personal and work abilities of the patient. Furthermore, the risk of chronic complications such as epilepsy, dementia and risk of falls is increased. Family members may need to assume the role of caregivers. The result is increased cost to the country for healthcare and rehabilitation amongst other, and loss of productivity .(4). In low income countries such as Uganda, impaired hand function proved to have the greatest impact on patients due to loss of ability to perform manual labour which is the most common source of income .(5)

The early treatment of acute ischemic stroke (AIS) potentially prevents these sequalae. It is a class one recommendation by the American Heart Association (AHA) that patients eligible for thrombolysis be thrombolysed within 3-4.5 hours (criteria applicable for exact time period) of symptom onset .(6)

Barriers to accessing the required level of care within this time period are sometimes present. These may be prehospital or in-hospital. Prehospital factors such as mode of transport, lack of knowledge about acuity and symptoms of stroke in the community, and attempting to contact a physician instead of going to the hospital have been identified as delays. (7) In addition to this, a review of access to healthcare in South Africa recently revealed inequity amongst various groups. Availability and affordability are barriers to people accessing healthcare timeously. (8)

Various modalities have been explored for targeted intervention to prevent prehospital delays. These include community education on early presentation, optimising emergency medical service (EMS) transport and response times, and optimising hospital systems. (9) Others interventions identified as beneficial are dispatcher recognition of stroke. (10), use of prehospital stroke screening tools by EMS. (11), and prenotification of patient arrival to hospital by first responders. (12)

Due to this high level of mortality and significant morbidity as a result of strokes, early intervention may prevent significant stresses upon families as well as health care facilities and society. Many patients following a stroke require assistance with ADLs and potentially nursing care thereby increasing the burden on the family, health department, and social services.

Motivation

Timeous intervention is the most important factor with regards to interventional treatment and clinical outcomes. (13) Early presentation allows for prompt assessment and treatment. Currently in the Western Cape there are no prehospital guidelines with regards to stroke management. With prehospital factors being a major contributor to delays in treatment. (13) Identifying how stroke patients present to a district health care facility would aid in recognizing the reason for delays and where intervention would be required. In developing health care systems prehospital delays have been cited as a cause for low thrombolytic use. (14) A number of factors have been shown to influence time to hospital presentation, demographics, history of cardiovascular disease, socioeconomic status, mode of transportation to hospital and clinical status. (14) In appropriate patient populations, early recognition of signs and symptoms as well as transport via EMS would have the greatest impact of increasing thrombolytic therapy. (15) Stroke education and public awareness of stroke symptoms improve access to stroke care. Accurate and timely identification of stroke by EMS control and providers, with early identification of stroke patients is a key factor to improving time from symptom onset to presentation. (13)

Aim

To describe the factors that influence time from symptom onset to hospital arrival in patients that present to a district level hospital Emergency Centre with confirmed ischaemic strokes.

Objectives

1. To describe the demographics of patients with confirmed ischaemic strokes that present to a district level hospital

2. To describe and compare their method of arrival (EMS, own transport, etc.) and type of referral (general practitioner, self-referral or primary health care referral).
3. To describe the location of the onset of symptoms (home, work, etc.)
4. To describe the time from the onset of symptoms to the time of arrival at the hospital, subgroup analysis will be performed to analyse potential confounders.
5. To describe the call details for all patients transported via EMS from home (including event times, triage category and chief complaint or working diagnosis to assess whether a stroke was clinically suspected or not (binary)).

Methodology

Study design

This study will be a descriptive analysis, using a retrospective folder and database review as data collection method.

Study setting

The study will be conducted at Mitchells Plain hospital, a district level hospital in the Mitchell's Plain Health District of the Metro Region, which is approximately 32km from Cape Town's city centre. The hospital serves a population of approximately 750 000 - 800 000, which includes the population of Mitchells Plain and the greater part of Philippi, a large nearby township. The demographics of Mitchells Plain comprises of low- to middle-income (LMIC) families of which 90% are coloured, and Philippi which is a low-income community that comprises of 90% black residents. The Mitchells Plain Emergency Centre (EC) attends to an average of 4250 patients per month, including adults and paediatrics, with a strong burden of diseases of lifestyle as well as HIV/TB and trauma.

Study population and sampling

All adult patients with a confirmed ischaemic stroke presenting to Mitchells Plain Hospital during the study period of 12 months (1st of January 2019 to 31st December 2019), will be eligible for inclusion.

Inclusion criteria

1. Adult patients (18 years and older) with confirmed ischaemic strokes on Computed Tomography (CT) Brain who presented to Mitchells Plain Hospital Emergency Centre in the study period.
2. Data from serial/consecutive patients will be collected for a period of (12 months) 1st January 2019 to 31st December 2019.

Exclusion criteria

1. Patients with stroke mimics.
2. Patients who did not have a CT brain.
3. Patients transferred from private Emergency Centre's.
4. In-hospital ischaemic strokes, patients already admitted who have a CVA during admission.

Data collection and management

Data will be collected in three stages:

Stage 1: Identifying participants who presented during the stipulated timeframe of 1st January 2019 to 31st December 2019 with an Ischaemic stroke.

In the first stage, using the Hospital and Emergency Centre and Tracking Information system (HECTIS)* database, a search will be conducted using International Classification of Diseases 10th revision (ICD-10) for the clinical diagnosis of a stroke. At this stage, all those who meet the aforementioned criteria will be selected. Deidentification of data will take place and only folder numbers and demographics will be collected. This is necessary to link the HECTIS data with the other databases.

Second stage: the Mitchells Plain Picture archiving and communication system (PACS) will be reviewed for patient identified in stage one of the data collection process and their CT Brain scan reports will be scrutinised to identify those that meet the inclusion criteria. Following stage one and two a full list of patients, deidentified, will be complete with folder numbers and demographics.

In stage three, using the folder numbers, Enterprise Content Management (ECM) will be reviewed to obtain the clinical variables and ETriage will be used to obtain data from Emergency Medical Services (EMS) transfers.

* HECTIS: Hospital and emergency Centre Tracking Information System, an official Western Cape Department of Health Application, is being used instead of the paper-based patient register to track patients presenting to the emergency centre. HECTIS was primarily designed for administrative and management purposes in order to streamline and track patient processes in the Emergency Centre (EC), including their process times, triage scores, diagnoses and dispositions. The data contained therein is useful source data for applied research relating to EC processes and flow. A patient gets registered on the database as soon as the patient registers an emergency centre visit on Clinicom. Patient details are pulled from the Clinicom database to minimise duplication of information. Thereafter the triage process (done by nurses) is documented on the system, including all the patient tracking information (which room or treatment area patient is in or moved to) and the process times. The doctors add the diagnosis via ICD-10 codes and the disposition (admitted, discharged or referred etc.). All process times are also documented automatically. The application will contain a list of the available variables that are routinely collected into HECTIS and indicates which of those variables will be available to request for research purposes. The variables fall into a number of broad categories:

- The EC register and audit

- ICD Chapter and diagnosis
- Triage TEWS and Tasks

This register is used in real-time by all nurses, all doctors and all clerks in the emergency centre and is securely accessed by individual username and password that provides permissions according to category of user. The application and database servers are only available on the Western Cape WAN or via VPN.

Data is entered routinely for every patient in the EC and no consent for research purposes is requested. HECTIS was primarily designed for non-research purposes to replace the old paper-based registers. We are applying for a waiver of consent for this research analysing data in HECTIS. Researchers will only be able to access the data on HECTIS if ethical and facility approval is granted. Extracted data will be deidentified and analysed anonymously at the group level, and therefore poses negligible risk to potential research participants. The waiver of informed consent will not adversely affect participants' rights and welfare, nor will it influence the level or type of care received by the individual participants. Given the distressed nature of patients entering the healthcare system through the emergency centre, and the time sensitive nature of their medical care, obtaining informed consent in the emergency centre is not feasible. This is the only electronic database that captures patient information on triage, diagnosis, process times and dispositions. This research is therefore not practical without a waiver of informed consent.

The HECTIS is a clinical record subject to regulation under the POPI act. Data collection is ongoing, and the data will be maintained indefinitely in the registry. Extracted, deidentified data used for research purposes will be securely stored as per the approved protocol outlined in each request for research access received. Broadly, we will recommend that extracted data used for research purposes be kept securely for 5 years before it is deleted.

The Master database is hosted at SITA Observatory; The Disaster Recovery Site is hosted at SITA George (Oracle 12C database URL: healthp-db.sita-cloud.westerncape.gov.za; Database Instance Name: HEALTHP Port:1526). Currently, the following EC's utilise the HECTIS application: Mitchells Plain Hospital EC, Heideveld Hospital EC, and George Hospital EC. Groote Schuur Hospital EC (C14) will be moving onto the application shortly, and a number of other ECs are in the process of rolling out the application.

Authorised application users can access the data via the HECTIS application. Users of HECTIS are granted access and authorisation according to their clinical role, e.g. a clinician will access a different part of HECTIS than a triage nurse. All users login via an active-directory authenticated login and password. The student will be responsible for the entire data collection process.

Missing or incomplete records

Cases will be excluded if patients' clinical data or information is missing or inaccessible. The number of missing cases will be clearly described and as well as much as possible of the relevant descriptive details (demographics, etc.). This will allow for comparison between cases and missing data. The investigators will make every effort to prevent missing data, including meeting with ECM of PACS administrators to try and minimise missing / lost data. A flow chart of cases and missing data/incomplete records will be presented.

Because this will be a descriptive study and because it will not be testing a hypothesis, incomplete data will be included and described up to the point where it can no longer be analysed. This will clearly be documented and described. Demographics will be presented for both missing and incomplete data so that it can be compared to those with complete data. The expected effect is described in the limitations section.

Variables and data sources

See Table 1 for a description of all variables that will be collected, as well as the data sources.

Data safety and monitoring

No identifying data will be collected. Initially the patient's folder number will be obtained from the HECTIS database (which will be necessary to tract the patients PACS and ECM records), thereafter the demographics and clinical data will be collected. The data will be de-identified from this step onwards. A study number will be given to each patient and thereafter only study numbers will be used. Names and folder numbers will be saved against study numbers in a separate file in cases of a query. Only study personnel will have access to the files, and it will be password protected and saved in a university computer at UCT, which will also be password protected. Also, information obtained will be backed up in a cloud server which will also be password protected and accessed only by study investigators.

Data analysis

A sample size of around 350 is anticipated considering the data from an unpublished study at Mitchells Plain Hospital by Mayet et al, that described the demographic of all patients with CT-confirmed strokes and calculated the prevalence of atrial fibrillation in the cases. Descriptive statistics will be used to describe demographics and categorical variables and proportions and percentages will be tabulated. Categorical variables will be analysed for non-random associations by using the Chi^2 test or the Fisher's Exact Test, depending on the characteristics of the variables. Continuous variables will be analysed for non-random associations with the help of the Student's T-test or a non-parametric alternative,

depending on whether the distribution is normal or not. Variables and statistical tests that will be used is summarised in Table 1 (below). Confidence intervals will be provided when necessary and statistical significance will be defined as having a $p<0.05$. Microsoft Excel will be used to collate data initially and SPSS Version 26 will be used to do the analysis.

Table 3: Data analysis plan

Objective	Variable	Variable category	Data source	Data analysis
1. Demographics of patients with ischaemic stroke	a) Age b) Gender c) Income status	a) Numerical, continuous b) Categorical, nominal c) Categorical, nominal	a) HECTIS b) HECTIS c) Clinicom/ Folder review (ECM)	Descriptive statistics, proportions and percentages, Fischer's Exact Test or Chi^2 Test
2. Method of arrival and type of presentation	a) Method of arrival b) Type of presentation	a) Categorical, nominal b) Categorical, nominal	a) HECTIS b) HECTIS	
3. Location of onset of symptoms	a) Location	a) Categorical, nominal	a) Folder review (ECM)	
4. Time of onset of symptoms and time of arrival at hospital	a) Time of onset of symptoms b) Time of arrival at hospital c) Time of triage at hospital d) Time of consultation at hospital	a) Numerical, continuous b) Numerical, continuous c) Numerical, continuous d) Numerical, continuous	a) Folder review (ECM) b) HECTIS c) HECTIS d) HECTIS	Student's T-test or non-parametric alternative
5. Description of EMS call data	a) Time of call b) Time of arrival at patient c) Scene time d) Time of arrival at hospital e) Chief complaint/working diagnosis	a) Numerical, continuous b) Numerical, continuous c) Numerical, continuous d) Numerical, continuous e) Categorical, dichotomous	a) ETriage b) Folder review (ECM) Private ambulance slip	Student's T-test or non-parametric alternative and Fischer's Exact Test/Chi^2 Test

Ethical considerations

Ethical approval will be sought from the University of Cape Town (UCT) Human Research Ethics Committee (HREC) prior to the implementation of the study. Thereafter, approval from the institution via the National Health Research Database (NHRD) will be applied for.

Risk to patients

Routine clinical data will be collected retrospectively, and patient care will thus not be affected in any way. The research project will de-identify the data in the very beginning of the data collection period and therefore poses minimal risk to the participants. Data will also be aggregated, and no individual data will be published and reported on. By including the clinical data of participants, it will in no way affect the rights and welfare of participants. A waiver of written consent will therefore be applied for.

Risk to community

This project will only benefit the community of Mitchell's Plain. It may become the basis of future research to improve the plight of the at-risk population with regards to improving access to stroke care. This study poses no risk to the community.

Risk to clinician

No data regarding clinician involvement will be recorded, no risk to any clinicians involved

Risk to institution

No identifiable risk to institution, data will be deidentified.

Limitations and strengths

Limitations

The accuracy and availability of clinical details depends on record keeping and because the data collection process is based on a retrospective review, incomplete or missing variables are expected. The investigators will aim to minimise this by scrutinising all the databases and triangulating information to ascertain the correct or missing information. Even though the investigator will clearly describe and present the demographics of the missing / incomplete data, it may affect the outcome and conclusion if the number of missing data is significant (>5%). This potentially will result in a smaller sample size and therefore decrease the power of the study, introducing a selection bias. The investigator will try to

prevent missing or incomplete data as far as possible. Missing or incomplete data will be presented in as much as possible detail, to allow for comparison with cases.

Not all patients with an ischaemic stroke undergo a CT scan because of resource limitation and this will affect the sample size and potentially cause selection bias. Even though this will likely cause a non-differential misclassification the sample size should be big enough to accommodate this.

This study only describes the population that presents to a district level hospital with an ischaemic stroke and does not include the broader health system. The study results will therefore be externally valid to only a certain cohort of facilities/scenarios.

Strengths

This is one of the first studies of its kind in the Western Cape and a reasonably big study with regards to numbers of participants and power of measurements. The information gained from this study could form the basis for future studies and help inform policies and guidelines regarding prehospital practices and access to stroke care.

Budget and resources

Budget

A total budget of R1 300 will be carried by the research team.

Resources

Hardware required: Laptop, External Hard drive (available – no cost)

Software required: Word processing software, referencing software, data management software and statistical analysis software- available (university licenses access - nil cost)

Access to database: HECTIS, PACS, ETriage, ECM

Table 4: Budget

March 2020 – April 2021				
Item	**Description**	**Unit cost**	**Nº of Units**	**Total cost**
Consumables				
1. materials and supplies				
2. materials and supplies				
3. specialised services				
4. office supplies, printing & reproduction for data collection	Stationary-pens, notepads, files			R500
5. office supplies, printing & reproduction for reports	Printing-data collection, reports, paper			R300
Research travel				
1. travel to sites	Travel to MPH: x 5 trips = 30km x 10 = 300km = +/-R400 (SARS rates)			R400
2. other, specify	Travel to UCT library: 5 trips= 5km x 10= 50km			R100
Minor research equipment				
1.				
2.				
3.				
Sub-Total				
Total				**R1300**

Project timeline

Table 5 Projected timeline

	Mar‘20	Apr’20	May‘20	Jun‘20	Jul‘20	Aug‘20	Sep‘20	Oct‘20	Nov‘20	Dec‘20
EMDRC	X	X	X	X						
Ethics			X	X	X					
Hospital approval (NHRD)					X	X				
Data collection							X	X	X	
Data analysis								X	X	
Write up									X	X
	Jan ‘21	Feb‘21	Mar‘21	Apr‘21						
Write up	X	X								
Submission			X	X						

Data dissemination plan

A publication in a peer reviewed journal is expected.

This study will provide insight into how patients with acute stroke seek emergency care. It will provide us with information regarding the transport and time delays that is associated with their trip to the hospital and can be used to improve prehospital services, as well as clinical guidelines and policies in the future. This is the first study of its kind and information regarding this topic has largely been anecdotal or based on smaller audits. The results of this study will be presented to the hospital and greater Emergency Medicine fraternity (faculties), as well as presented to provincial role players. It may well alter prehospital practices and future guidelines.

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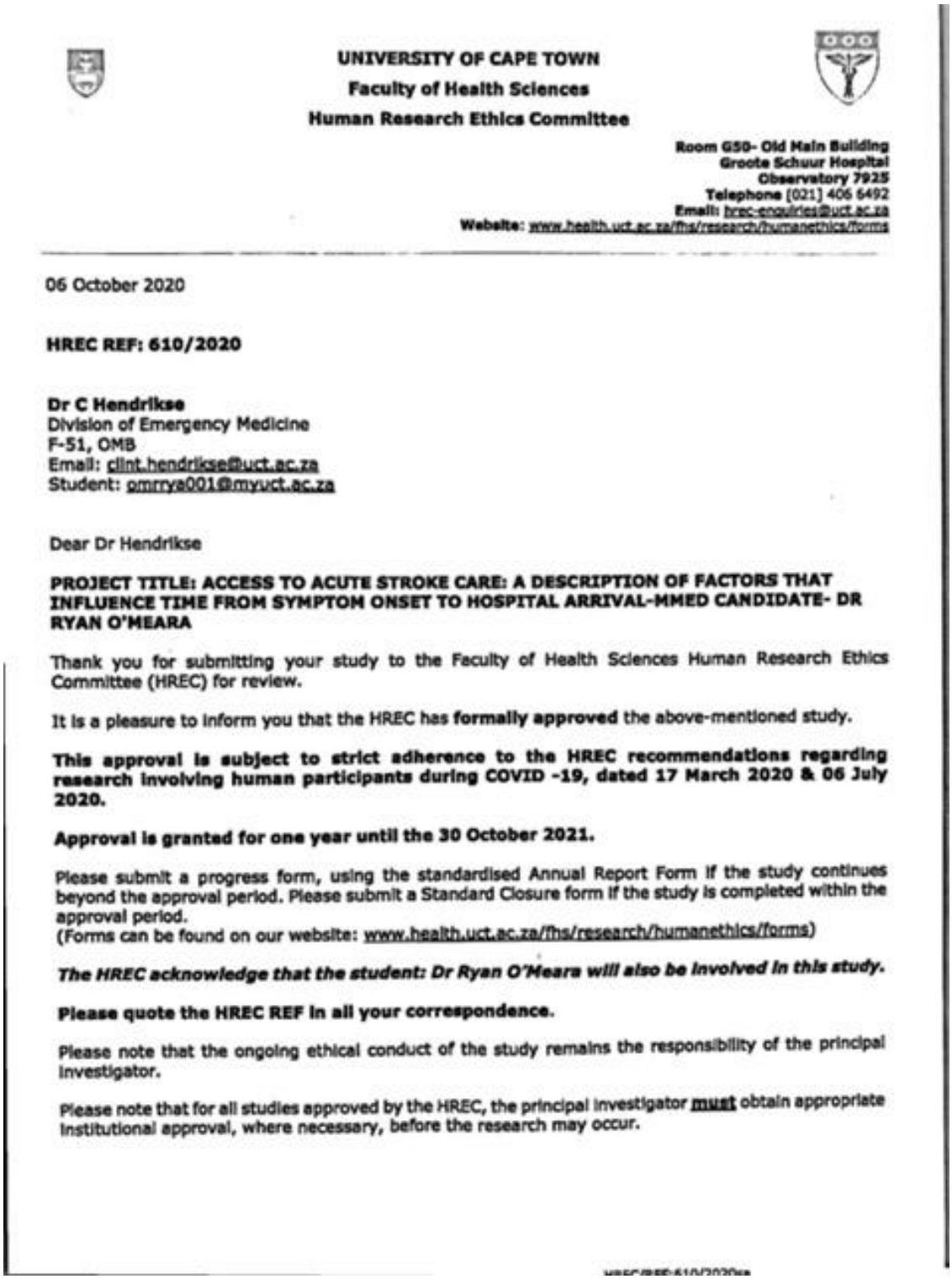
Addendum 4: HREC Approval Letter



UNIVERSITY OF CAPE TOWN
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Human Research Ethics Committee

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06 October 2020

HREC REF: 610/2020

Dr C Hendrikse
Division of Emergency Medicine
F-51, OMB
Email: clint.hendrikse@uct.ac.za
Student: omrrya001@myuct.ac.za

Dear Dr Hendrikse

PROJECT TITLE: ACCESS TO ACUTE STROKE CARE: A DESCRIPTION OF FACTORS THAT INFLUENCE TIME FROM SYMPTOM ONSET TO HOSPITAL ARRIVAL-MMED CANDIDATE- DR RYAN O'MEARA

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 October 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Ryan O'Meara will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF:610/2020sa