Factors Influencing Pre-Hospital and In-Hospital Delays at Time-To-Treatment and Complications in Stroke: A Prospective Cohort Study

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Abstract

Background: The results of acute ischemic stroke (AIS) are highly affected by time-to-treatment. This study aimed at determining the factors influencing the in-hospital and pre-hospital delays in the complications and time-to-treatment in AIS.

Methods: The present prospective study was carried out on 204 AIS patients referring to the stroke care unit in Zanjan, Iran (2019). To collected the required data, the patients and families were interviewed, as well as using the observations and records. The complication and mortality rates were recorded for 30 days after stroke via call follow-ups.

Results: Based on the obtained results, the maximum delay was associated with the onset-to-arrival time (288.19 ±339.02 minutes). The logistic regression results indicated a statistically significant decline in the treatment via consultation after initiating the symptoms, transferring the patient to the hospital via emergency medical service, and the patients' comprehension regarding the AIS symptoms. It was also found that an increase in the onset-to-treatment time (P <.001) and higher National Institutes of Health Stroke Scale (NIHSS) scores (P< .001) are the most critical factors related to the post-stroke complications. The higher age (P <.044) and NIHSS scores (P < .001) were considerably related to the mortality in AIS patients.

Conclusion: It is essential to inform people regarding AIS indicators and referring to AIS treatment units to reduce the treatment time.

Background

Stroke is one of the most prevalent neurological complications (1). This health problem annually affects 15 million people worldwide, of which one third suffer from a permanent disability and one-third ultimately die (2). The age of acute ischemic stroke (AIS) occurrence in Iran is 10 years earlier in comparison to that of the developed countries (3, 4). In the early hours, AIS is a medical emergency requiring critical treatment and care because auspicious results can be obtained by its fast diagnosis and proper interventions. Furthermore, delayed treatment can lead to considerable complications, higher mortality, and heavy expenses for the person, families, and the community health system (5, 6).

The most effective approach to treat AIS patients is reestablishing and recanalization of blood flow to the brain tissues (7–9) using non-invasive and invasive treatments. In these processes, the blocked vessels are reopened using recombinant tissue plasminogen activator (rTPA) and mechanical devices (angioplasty) (10, 11).

Using recombinant tissue plasminogen activator (rTPA) was recommended by the Food and Drug Administration (FDA) in 1996, in AIS patients over the first 3 hours of starting the symptoms (12). Moreover, American Stroke Association Standard (2018) suggests brain imaging within < 20 min, the interval of < 60 min between the thrombolytic therapy and hospital arrival for over 50% of patients

qualified for rTPA (13). The reduction of 15% in door-to-needle (DTN) time of the patients in administering thrombolytic therapy is related to the improvement of 4% in clinical symptoms and reduction of 5% in mortality rate in AIS patients (14, 15).

Notably, rTPA is not used due to wasting the golden time of medication utilization because of the delayed referring to the hospital (16). The time-to-treatment delay in AIS patients may be caused by different factors such as pre-hospital and intra-hospital reasons. Delays in recognizing patients and their transfers are regarded as the pre-hospital causes. Meanwhile, delays in neurologic visits, delays in decision-making in the treatment procedure, and delays in brain imaging are denoted as intra-hospital delays causes (17, 18). In a study in Iran, rTPA was not provided for 80.2% of patients due to a delay of longer than 4 hours and 30 minutes. The delay in hospital referral was the main cause of the delay for such patients (19). Another work in Iran found the mean CT scan and arrival time of the patients to the hospital as 91 minutes, which is 66 minutes higher compared to the international rules. Moreover, the mean arrival time and getting rTPA was 147 minutes, which is 87 minutes higher than proposed by the international guidelines (20). In the USA, in a study, at least an operative delay factor was recognized in 84.3% of patients, with the maximum delay associated with the imaging (21). The average onset-to-arrival time was 147.2 minutes in another study in Egypt, along with the meantime of 87 minutes between the rTPA injection and hospital arrival. The longer distances from health centers and misperception of stroke symptoms were the main reasons for the delay in these patients (22).

Various factors have still a role in treatment delays, such as the patient's delay after the early symptoms of onset and treatment staff delay. In every community, it is imperative to investigate the factors affecting the recognition of factors for pre-hospital and in-hospital delays, the quality-of-care delivery services, as well as the timely treatment-effective individual factors. The stroke code (Code 724) was announced by Iran's Ministry of Health to the medical universities in 2016 to manage the stroke patients' treatment well. Thus, followed by implementing this plan, it was felt essential to review the status of pre-hospital and hospital delays in Stroke Care Units (SCU) in Iran. Furthermore, to the best of the authors' knowledge, no study exists in Iran investigating the delays in-hospital and in pre-hospital simultaneously after running Code 724. Therefore, this study aimed at determining the factors influencing pre-hospital, in-hospital, and time-to-treatment delays in acute stroke and their associations with mortality and complications.

Methods

This cross-sectional descriptive study was performed at the SCU from July to the end of October in 2019 in Zanjan City (Iran).

Study setting

Zanjan province with the capital of Zanjan city is placed in the northwest of Iran. It includes a population of 105,7461 people, 978 villages, and8 towns. It possesses 10 hospitals connected to Zanjan University of Medical Sciences. Nevertheless, only one stroke care department (in Vali-Asr hospital in Zanjan University of Medical Sciences) in the city provides services for ischemic stroke patients.

SCU in Zanjan established at Vali-Asr Hospital was known as the stroke treatment center in 2016 in Zanjan Province. In Iran, Code 724 is referred to the stroke patients in whom less than 4 hours and 30 minutes have passed since initiating the stroke symptoms. Based on this code, once calling Emergency Medical Services (EMS) by the patient, he/she is asked about the Face-Arms-Speech-Time (FAST) of the symptoms. Then, after transferring the ambulance to the bedside of the patient, the FAST symptoms are examined by the emergency technician, and the SCU is reported followed by confirmation. The patients around the province are immediately transferred from all medical centers to the SCU in that province. After transferring to the hospital, a neurologist examines the patient at the triage unit and send him/her to the CT scan unit when diagnosing a stroke to administer the rTPA medication there.

Sampling

This study was performed for AIS patients in the SCU of Zanjan. The samples were collected based on a convenience sampling method. The participants of the study included patients referring to the SCU during the sampling interval who met the inclusion criteria. According to the pilot study on 20 AIS patients, the sample size of 181 was considered with an effect size of 0.05, a sampling error of 20 minutes, and a confidence level of 95%. In this study, 204 patients with AIS referring to the SCU were assessed.

Data collection

The data were collected through interviews with patients and observation, as well as with their families, if necessary. The statistical research population included the patients referring to the stroke ward at Val-Aasr Hospital in Zanjan. Then, a questionnaire was completed associated with the demographic information and the time interval from the start of primary symptoms to the onset of therapeutic interventions. Two researchers monitored the patients 24 h a day during a hospital stay. The researchers made follow-ups for the patients in the ICU of the neurology unit and SCU, as well as 30 days after discharge. A researcher-made questionnaire was used to collect the data and identify the information on demographic features and factors influencing the time-to-treatment and the average period of symptoms onset for treatment. The questionnaires included three sections. The questions regarding the demographic features of the patients were included in the first part. The second part contained questions regarding the pre-hospital delays' reasons. The third part is comprised of questions about the reasons for the in-hospital delay (Appendix No. 1). The complications frequency was checked using a list of prevalent complications followed by acute strokes in terms of stroke-related papers. The checklist included 28 stroke complications totally checked for one post-acute stroke month (Appendix No. 2). Mortality and complications during hospitalization were recorded through post-discharge phone calls with patients or their families and observation. In case the patient died after discharge, his/her medical record was checked for determining the stroke-associated reasons for complications and death. The treating physician approved these data. To assess the AIS severity, the National Institutes of Health Stroke Scale (NIHSS) was considered. This tool includes 11 items, for which a score of 0 denotes the individual's average performance in the studied field, and a score of 4 represents the maximum impairment in this concern. The maximum and minimum scores on this scale are 42 and 0, respectively. In this regard, the

score 0 denotes lack of stroke symptoms, 1 to 4 is mild stroke, 5-15 is moderate stroke, 16-20 is moderate to severe stroke, and 21-42 denotes severe stroke. In-hospital mortality rates were examined through observation and mortality rates of 30 days by making phone calls with patients or their families.

The questionnaire validity was determined based on content validity. The designed questionnaire was offered to 10 experts to make the essential modifications and alterations in terms of their ideas. The reliability was assessed using the evaluators' reliability. The questionnaire was simultaneously completed by two researchers for 10 patients. Then, Cohen's kappa coefficient was assessed between the information of the researchers-completed questionnaire and the evaluators' reliability was approved by achieving K = 0.973. The reliability and validity of the NIHSS tool were confirmed by Kasner et al. (23).

Ethical considerations

This study was approved by the Ethics Committee of Zanjan University of Medical Sciences by the Ethics Code of IR.ZUMS.REC.1398.095. All methods were performed in accordance with the relevant guidelines and regulations. The inclusion criteria of the study were described by the researcher to the patients or their families, and written consent was acquired. The participants were guaranteed the confidentiality of all their information and the right for leaving the study at any time.

Procedures

The patients referring to the SCU were chosen based on the inclusion criteria. The researcher completed the 60-item questionnaire after treatment and relative stabilization with the assistance of the patient or his/her caregivers. The complications were assessed and evaluated using the prepared checklist. It was completed within 1-4 weeks followed by acute stroke. The mortality and complications were evaluated during the hospitalization and through telephone calls after discharge.

Variables

The variables in this research were stroke risk factors, demographic variables, affective factors associated with in-hospital and pre-hospital times for starting treatment, mortality, and complications. Moreover, the stroke complications were regarded in terms of the existence of at least one complication on the checklist. The mortality rate was evaluated regarding stroke complications in the hospital and 30 post-hospitalization days.

For mortality occurring within 30 days of hospitalization caused by AIS, the medical records of the patients need to be revised for determining the AIS mortality causes.

Data analysis

SPSS V.16 was used to perform statistical analysis. The data were distributed in terms of the normalized central limit theorem and sample size. The factors related to the delay in treatment and those related to

mortality and complications were investigated using logistic regression. In this study, the significance level was considered to be less than 0.05.

Results

This study was conducted on 230 patients with stroke referring to the SCU from early July to late October 2019. The data of 16 patients with transient ischemic attack and 10 patients with hemorrhagic stroke were excluded from the study. Ultimately, the data of 204 acute ischemic stroke patients referring to the SCU were assessed. The ischemic stroke in these patients was diagnosed by the treating physician.

In total, 204 patients were included in this research, of which 55.9% were men, 19.6% possessed a high school diploma, and 72.5% were illiterate. The participants' mean age was 68.99 ±13.91 years. Fifty percent of the patients lived in Zanjan. Based on the patients' statements, 87.7% of them had at least one risk factor and 54.4% had no sufficient income. Hypertension (59.3%) was the most usual risk factor for AIS, and ischemic heart disease was in the second rank (30.4%). Moreover, about 77.9% of the patients were at home when initiating the symptoms.

The severity of the stroke was moderate in 52% of the patients. The mean hospitalization duration was 6.48 ± 5.64 days. In this study, 140 (68.6%) patients were referred to the SCU with code 724. They arrived at the hospital within less than 4 hours and 30 minutes after the symptoms' onset. Moreover, rTPA was provided for 129 (63.2%) patients, but it was not presented for 75 (36.8%) patients. The reason for not injecting rTPA in 64 patients (31.4%) was the delay over 4 hours and 30 minutes from the symptoms' onset to referral to SCU. After the first month, 38 (18.6%) patients had at least one complication and 31 (15.2%) patients died.

In this study, 70.6% of the patients regarded their prime symptoms as other disease symptoms, while not believing in a stroke. Furthermore, 17.2% had no consultation with anyone after the onset of the symptoms and took no action. After the onset of symptoms, about 47.5% of the patients referred to medical centers rather than SCU, and they mostly (30.4%) referred because of availability or proximity. Moreover, 46.1% referred to SCU through personal vehicles. A neurologist performed the first visit for more than half of the patients (62.7%) (Table 1).

In the present study, the mean onset-to-arrival time and the mean onset-to-treatment time were 288.19 ± 339.02 minutes and 314.13 ± 341.04 minutes, respectively. Within the pre-hospital delay factors, the delay when making a decision to contact the Emergency Department or the effort to refer to medical centers (204.74 ± 321.38 minutes) was longer compared to the time of patient transfer to the hospital (83.52 ±72.38 minutes) (Table 2).

In the present research, the predictors of the onset-to-treatment time were investigated using logistic regression. In logistic regression, the absence or presence of delay in arriving at the hospital is regarded as the dependent variable. The patients referring to the SCU within 4 hours and 30 minutes were considered with no delay and the patients referring to SCU after this time were regarded as with delay.

The logistic regression results indicated that consulting with an individual referring to the Emergency Department after the symptoms onset and appropriate comprehension of the patients about the stroke symptoms were the robust predictors of shortened delay until treatment initiation (Table 3). Based on the results of logistic regression, the increased onset-to-treatment time and higher NIHSS scores were the most significant predictors of complications (Table 4). Furthermore, higher NIHSS and age scores were the most important predictors of stroke caused mortality (Table 5).

Discussion

Our results indicated that pre-hospital delay was longer compared to the hospital delay. The delays in the effort to refer to the medical treatment or the decision to call the Emergency Department were compared to the time of patient transfer to the hospital.

Along with our study, Ghiasian et al. in a study in Hamadan (Iran) reported that the time of symptoms onset to arrival to the hospital was 282 minutes, while it was 192 minutes in the study of Griesser et al (24, 25). Nevertheless, in the study of Ayromlou et al. in Tabriz (Iran), this time was 916 minutes, which is not in line with our results (20). In the study of Ayromlou et al., which was conducted in the metropolitan area of Tabriz, the delay in the patients' arrival could be caused by traffic problems in this city. In the smaller towns around the provinces equipped with SCUs, accurate diagnosis of the stroke, the existence of neurologists, and administering thrombolytic medication can lower the onset-to-treatment time dramatically.

In the study of Ruiz et al. in Spain, the mean onset-to-arrival time was 201 minutes while the mean onset-to-decision time was 72 minutes (26). Furthermore, in the study of Faiz et al. in Norway, these times were 179 minutes and 92 minutes, respectively (27). In contrast with our study, in these two studies, there was a shorter delay in decision making.

Koksal et al., Ruiz et al., Faiz et al., Sobral et al., Springer et al., and Haiqiang et al. showed that access to transfer with EMS shortens the delay in hospital arrival (26-31). In our study, less delay was also experienced by the patients referring to EMS. Moreover, the patients were mostly referred to other treatment centers because of the availability or proximity or referred to SCUs late owing to disregarding the preliminary symptoms. Examining the stroke symptoms by EMS technicians might be a useful step toward faster transfer of these patients to the hospital.

Consistent with our study, the findings of studies conducted in America, Asia, and Europe indicated that absence of awareness of stroke symptoms, patients' beliefs and misconceptions about the prime symptoms, and failure to consult an individual after the onset of the symptoms resulted in longer delays in hospital arrival and time-to-treatment for stroke patients (22, 24, 26-29, 31-33). The results indicate that consulting with others after initiating the symptoms may be useful to prevent a delay in cases the symptoms of the patients are not well-recognized or seriously-taken.

The results of our investigation on the hospital delay factors in AIS patients revealed that there were no delays in AIS patients receiving Code 724. In this study, the interval between hospital arrival interval to rTPA implementation (25.18 ±17.01 minutes) and between hospital arrival to brain CT scan (10.60 ± 6.79 minutes) was much shorter compared to the time proposed by the American Stroke Association guidelines (13). In the study of Huang et al. in China, the mean CT scan time was 28 minutes, the mean time to first visit patients according to Code 724 was 10 minutes, and the mean rTPA injection time was 116 minutes (34). In the study of Hsiao et al., the mean time to first visit was 6 ± minutes, the mean patient arrival time to thrombolytic injection was 63 ± 23 minutes, and the mean time of arrival to brain imaging was 11 ± 7 minutes (35). Ayromlou et al. in Tabriz, Iran, found the mean time of CT scan and patients' arrival to the hospital as 91 minutes, which was 66 minutes longer than the international guidelines. Moreover, according to their results, the mean time of hospital arrival of the patients and receiving rTPA was 147 minutes, which is 87 minutes longer than that recommended by international guidelines (20). In the study of Dhaliwal et al. in the US, the mean initial CT scan time was 13.66 minutes, the CT scan interpretation time was 25.20 minutes, and the time between rTPA injection and the arrival of the patients was 51.27 minutes (36). Hasankhani et al. in Tabriz (Iran) found that the mean time between hospital arrival and rTPA injection is 69 minutes (19). In the study of Mowla et al. in New York, the maximum imaging delay was longer than 25 minutes (21). According to the findings obtained in Iran and other countries, the time between time-to-treatment and hospital arrival in patients with Code 724 is much longer compared to our results. It is indicated that the stroke code team management in stroke patients at SCUs could significantly shorten the time-to-treatment. In the present study, the onset-to-treatment time and the AIS severity were the best predictors for complications in stroke patients among the factors associated with one-month complications in patients. Furthermore, the severity of the AIS and higher age were the most significant predictors of mortality in AIS patients. Denti et al. in Italy found that the mortality risk was lower significantly among stroke patients referring to the hospital earlier. They also found a significant correlation between the severity of neurological score and pre-hospital delay with mortality rate. In this study, a better result was observed for patients with a stroke severity of less than 18 (37). In our study, a significant association was observed between the higher neurological score and mortality. In line with our study, Jung et al. in Georgia reported a better outcome for patients receiving rTPA in less than 45 minutes had within 90 days (38). In the study of Faisal et al. in Qatar, the complication rate reduced from 15.7% to 8.8% by decreasing the DTN time between 2008 and 2015 (39). Consistent with our results, Oliveira et al. in Brazil, observed a significant association between the mortality rate and higher age in stroke patients (40).

Conclusion

In the present study, a longer pre-hospital delay was found compared to hospital delay in case of stroke events. Among the pre-hospital delay factors, the delay in access to a medical center or deciding to call the EMS was longer than the time of patient transfer to the hospital. In other words, a larger portion of the delays in pre-hospital factors is caused by the delay in patients' decision to refer to the hospital. It appears that giving information to at-risk people, particularly those over 60 years, about the stroke risk

factors, the importance of rapidly initiating treatment to enhance the disease outcomes, and the early symptoms of stroke will help patients comprehend their symptoms properly. Hence, they will be transferred to the hospital faster by calling the emergency system.

Limitation

The lower accuracy of reminding the times, particularly by elderly patients, was one of the limitations of this study. The researchers tried to precisely record the times and factors influencing pre-hospital delays while highlighting the important times like news time, Azan time, and events of the day. Regarding the geographical and cultural position of Zanjan, the present results cannot be generalized to other communities.

Abbreviations

FDA, Food and Drug Administration; NIHSS, National Institutes of Health Stroke Scale; DTN, Door-To-Needle time; rTPA, recombinant Tissue Plasminogen Activator; AIS, Acute Ischemic Stroke; SCU, Stroke Care Unit; CT scan, computed tomography scan.

Declarations

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Authors' contributions

The study was designed by NH, the conducted statistical analyses of the data were included in interpreting the data, and the manuscript was written. The data were collected by NG including the data interpretation. MR D was included in interpreting the data. The final manuscript was read and approved by all authors.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to anonymity but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This work was performed after granting the approval of the ethics committee of Zanjan University of Medical Sciences with an ethical code (IR.ZUMS.REC.1396.305). Informed consent was obtained from study participants before the study in the declaration section.

Consent for publication

Not Applicable.

Competing interests

The authors declared no competing interests.

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Tables

Table 1. The frequency of subjects in terms of patients' perception of symptoms and their referral way to the medical centers

N (%)	Variables	
60 (29.4)	Neurology	Patient perceptions of early symptoms
144 (70.6)	Non-neurology	
49 (24)	Spouse	Consultation after the symptoms onset
94 (46.1)	Children	
4 (2)	Colleague	
18 (8.8)	Relatives	
4 (2)	Nurse	
35 (17.2)	Not consulting anyone	
107 (52.5)	Referral to SCU in Zanjan	Patient referral after symptom onset
55 (27)	Other medical centers	
28 (13.7)	Clinic	
13 (6.4)	Private office	
1 (0.5)	Private hospital	
62 (30.4)	Availability or proximity to the center	Reasons for referral to a treatment center other than SCU
8 (3.9)	Not awareness of stroke center at SCU	
27 (13.2)	Not considering the disease seriously by the patient	
94 (46.1)	By personal vehicle	Referral
64 (31.4)	By Emergency Services (EMS)	
44 (21.6)	Referral by ambulance from other medical centers	
1 (0.5)	Stroke inside the hospital	
1 (0.5)	Air Emergency	
2 (1)	General Practitioner	The first visitor of the patient
128	Resident of Neurology	

(62.7)	
68 (33.3)	Emergency medicine specialist
5 (2.5)	Neurologists
1 (0.5)	Non-neurology Resident

Table 2. The mean of the time interval between symptoms onset and treatment in terms of pre-hospital and in-hospital factors

Mean ± St. Deviation(minutes)	Confidence interval (minutes)	Variables	
204.74±321.38	160.38-249.10	Onset –to- decision time	**Pre-hospital time intervals**
83.52±72.38	73.53-93.52	The transfer time	
288.19±339.02	241.39-334.99	Onset –to- arrival time	
3.07±2.46	2.66-3.49	Door –to- examination time (code stroke)	**In-hospital time intervals**
10.6±6.87	9.39-11.82	Door –to –imaging time (code stroke)	
17.99±13.13	15.77-20.21	Door –to –SCU entry time (code stroke)	
21.87±13.94	19.57-24.18	Door –to- treatment decision making (code stroke)	
23.08±16.46	20.22-25.93	Door-to- order time (code stroke)	
25.01±16.97	22.05-27.96	Door –to- Needle time (code stroke)	
15.08±8.51	12.94-17.22	Door –to- examination time (No code stroke)	
214.98±193.49	166.65-263.32	Door –to –SCU entry time (No code stroke)	
29.07±33.82	20.33-37.80	Door –to –treatment time (No code stroke)	
314.13±341.04	267.05-361.21	Onset –to – treatment time in stroke patients	

Table 3. The predictors of symptom initiation to arrival to SCU

95% C.I.for EXP(B)		Logistic regression analysis						variables
Upper	Lower	EXP(B)	Sig.	df	Wald	S. E	B	
1.047	.929	.986	.646	1	.211	.031	-.014	Stroke Intensity (NIHSS)
.518	.036	.136	.003*	1	8.575	.680	-1.992	Patient perceptions of early symptoms
800.241	20.598	128.386	.000*	1	27.042	.934	4.855	Consultation after the onset of symptoms
31.155	2.250	8.372	.002*	1	10.045	.670	2.125	Transportation by Emergency medical service
3.194	.597	1.381	.451	1	.569	.428	.323	Sex
1.063	.988	1.025	.193	1	1.696	.019	.025	Age
5.734	.593	1.845	.290	1	1.120	.579	.612	Risk factor
		.010	.002	1	9.478	1.504	-4.631	Constant

*P-value< .05

Table 4. The predictors of stroke complications during one post-stroke month

95% C.I.for EXP(B)		Logistic regression analysis						variables
Upper	Lower	EXP(B)	Sig.	df	Wald	S. E	B	
1.229	1.074	1.149	.001*	1	16.163	.035	.139	Stroke Intensity (NIHSS)
1.003	1.001	1.002	.001*	1	11.974	.001	.002	Symptom Onset-to-treatment time
		.036	.001	1	37.911	.541	-3.333	Constant

*P-value< .05

Table 5. The predictors of mortality a month after the stroke

95% C.I.for EXP(B)		**Logistic regression analysis**						Variables
Upper	Lower	EXP(B)	Sig.	df	Wald	S.E	B	
7.652	2.560	4.426	.001*	1	28.347	.279	1.487	Stroke Severity (NIHSS)
1.002	.999	1.001	.482	1	.495	.001	.001	Onset-to- treatment time
1.082	1.001	1.041	.044*	1	4.063	.020	.040	Age
		.000	.000	1	27.407	1.637	-8.568	Constant

*P-value< .05

Supplementary Files

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- AppendixBMCemergency.docx