VOLUME-8, ISSUE-11, NOVEMBER-2019 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Community Medicine

A STUDY TO ASSESS TRIGGER FACTORS FOR STROKE USING A CASE CROSSOVER DESIGN IN A TERTIARY CARE HOSPITAL OF NORTHERN INDIA

Dr Veenal Chadha Demonstrator, Department Of Community Medicine, Government Medical College And Hospital 32 ,chandigarh.

Dr Muzamil Nazir* Tutor, Department Of Community Medicine, Maharishi Markandeshwar Medical College Solan. *Corresponding Author

ABSTRACT

Background: With all that is known about stroke epidemiology, however, it remains extremely difficult, if not impossible, to predict when a stroke will occur, even among those with a heavy burden of risk factors.

Objective: To assess trigger factors for stroke using a case crossover design in a tertiary-care level hospital of Northern India .

Methods: The study was conducted on patients presenting with stroke to the department of neurology of Dr. RPGMC at Tanda in Kangra district of Himachal Pradesh for a period of one year starting from September 2015 to September 2016.

Results: Drug abuse, alcohol abuse, smoking, tea intake , fever, positive emotions , negative emotions and unusual physical exertion two hours prior to stroke associated significantly as triggers.

Conclusion: Trauma as a trigger was not significantly associated. Coffee intake, sexual intercourse and sudden posture change were not found to trigger stroke.

KEYWORDS : Trigger Factors, Stroke, Case Crossover

Stroke , characterized by a neurological deficit of sudden onset , typically due to brain infarction ("ischemic stroke") or, less often , intracerebral hemorrhage , represents the primary neurological cause of acquired disability in adults and a leading cause of death .[1] It is also a major contributor to cognitive decline and dementia.[2] While chronic risk factors for stroke are reasonably well understood, the acute precipitants, or triggers, of stroke, relatively remain understudied. [3]Recent studies have shown that ten risk factors are associated with 90 percent of the risk of stroke.[4]

In spite of this, it is impossible to predict when a stroke will occur, even in people with a high – risk profile.[5] The patterned occurrence with a morning peak of ischemic stroke onset further strongly suggest that the disease does not occur randomly.[3, 6] Vascular events could be precipitated by acute factors, called triggers, which increase the risk of disease over a relatively short period of time and may directly lead to its onset.[3] Some triggers may exert a single, sharp and short transient effect on the pathophysiological process, whereas,others may exert more varied and pervasive effects, probably amplifying risk at multiple points and over a longer period.[7]Thus, the period of time associated with an increased risk, called hazard period, starts more or less quickly after trigger initiation, and its duration may vary according to the type of trigger.[8]

With all that is known about stroke epidemiology, however, it remains extremely difficult, if not impossible, to predict when a stroke will occur, even among those with a heavy burden of risk factors.[9] Our knowledge of stroke precipitants, or triggers, to be contrasted with risk factors, remains relatively primitive. [9] Nonetheless , recent evidence suggests that predicting not just who is at risk of stroke ,but when stroke is most likely to occur, may be increasingly possible. Why does a given patient,perhaps one with a history of hypertension and diabetes mellitus for decades, have a stroke today? Is this short term risk of stroke a predictable or stochastic event? Can the stroke - prone state be measured in some way? If this state can be measured, and is therefore potentially predictable, is there something that can be done to prevent consequent stroke?

There are several potential triggers for stroke.[5] In MI, these factors are speculated to qualitatively alter the stable or quiescent phase of coronary atherosclerosis and initiate a cascade of events that culminates in plaque rupture and thrombosis leading to acute MI.[8]

Studies conducted on role of triggers have already demonstrated the role of physical exertion[10], anger [10],emotional and mental stress [11], sexual activity [12] or acute infection on myocardial infarction occurrence. [13] Studies have shown that anger, negative or positive emotions, and psychological distress were significantly associated with stroke onset. However, these associations have been identified in single study.[9]

Identification of a short-term state of elevated stroke risk could have several therapeutic implications. Patients with a history of stroke, or with significant burden of risk factors for stroke, might be targeted for more intensive stroke prevention during the period of increased risk (stroke triggers). It is with this intention of identifying, triggers for stroke that this study was done among patients presenting with stroke to the department of neurology, Dr. RP Government Medical College, Tanda.

Material and methods

1. Study Area:

The study was conducted on patients presenting with stroke to the department of neurology of Dr. Rajendra Prasad Government Medical College at Tanda in Kangra district of Himachal Pradesh.

2.Study period:

The study was carried out for a period of one year starting from September 2015 to September 2016.

Inclusion criteria:

Patients hospitalized for stroke diagnosed according to the diagnostic criteria as given under:

Diagnostic criteria:

Stroke was defined as a rapidly developing clinical syndrome of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than due to vascular origin. Only stroke survivors were included in the study.

Patients with recurrent strokes were eligible if they did not have previous significant disability (Modified RANKIN Scale - 2), and no more than two previous ischemic events, the last one 6 months or more before the present event.

Sample Size:
All consecutive cases fulfilling inclusion criteria were included in the study.

Exclusion criteria:
1) Patients not consenting for study
2) Patients with dementia (MMSE less than or equal to 24) and aphasia
3) Patients not able to identify time of onset of stroke symptoms
4) Too ill to complete interview
5) Poor memory around time of stroke
6) Comatose/stuperose/intubated patients
7) Patients with other form of stroke(venous thrombosis and aneurysmal bleed)

Design
The study design was case-crossover. A total of 24 hours before the onset of stroke was the study design frame for conduct of this study. This 24 - hour period before the onset of stroke was treated in the interview as one long hazard. Detailed data about exposures to potential triggers during the 24 hours before the onset of stroke was recorded. A 2- hour hazard period immediately before the onset of ischemic stroke was compared with the 2- hour control period at the same time on the day before onset of stroke. The interview for this purpose was made to elicit information from the patient with regard to potential trigger effects by direct interview. A questionnaire based interview was conducted for the purpose of eliciting information from the study participants .The information included details on socio demographic variables, personal and family history and history of stroke including details on potential triggers. The information was corroborated by conducting an interview with the nearest relative of the patient, who had been with the patient for last two days.

The study population was not well versed with english so PANAS scale was converted into hindi before eliciting information regarding positive and negative emotions.

Data collection :
Study unit was medicine ward both male and female at Dr RPGMC Tanda as admitted patients were included in the study. All the medicine wards were visited all days a week for 1 year starting from start of study period from September 2015 to September 2016.

Interview :
At medicine ward the patient and the attendant was interviewed face to face after explaining the study and its purpose and also after obtaining a written consent in hindi using a structured pilot tested interview based questionnaire for data collection. Data for universal characteristics like age, gender, residence, phone number and anthropometry were collected.

Definitions used in the study:
The positive and negative emotions were identified on the bases of the PANAS scale. The patients were provided with a list of emotions from the scale as outlined in Annexure 1.2 and asked to rank them on a scale of 1 to 5 with 1 meaning very slightly or not at all and 5 meaning extremely.

ACUTE ALCOHOL ABUSE:
Acute alcohol abuse was defined as alcohol intake of more than 40gm (equivalent to four standard drinks) within the 24 hours preceding stroke.

CLINICAL INFECTION:
The diagnosis of clinical infections was based on the presence of fever alone, typical symptoms alone or fever with typical symptoms. Subjects were classified as having antecedent infection present within last 24 hours and last 2 hours prior to stroke onset.

COFFEE CONSUMPTION:
Exposure to coffee consumption as triggering risk factor for stroke was defined as consumption of coffee during last 24 hours and last 2 hours preceding onset of stroke symptoms in infrequent drinker (less than one cup/day).

RECREATIONAL DRUG ABUSE:
Patients were enquired regarding use of recreational drugs (cocaine, amphetamine, heroin, marijuana and any other) and over the counter medications in last 24 hours and last 2 hours prior to stroke onset.

SEXUAL INTERCOURSE:
Sexual activity within last 24 hours and last 2 hours preceding stroke onset was enquired.

SUDDEN POSTURE CHANGE DUE TO STARTLING EVENT:
Patients were asked to recall any sudden change in posture during the last 24 hours and last 2 hours preceding stroke onset. For each reported sudden change in posture, the exact time and reason was specified. Only patients reporting sudden changes in posture in response to a startling event, such as getting up suddenly from bed in response to the patient's child/grandchild falling down and crying or getting up suddenly in response to an unexpected very loud noise, or in response to sudden forceful movements by barbers etc were considered as exposed.

TRAUMA/ SURGERY:
Subjects were enquired for motor vehicle accidents, sports injury and spinal manipulative therapy especially chiropractic neck manipulation during last 24 hours and last 2 hours preceding stroke onset. Subjects were also enquired for any major surgery (general and cardiac).

UNUSUAL VIGOROUS PHYSICAL EXERTION:
Subjects were asked about the frequency and timing of moderate exertion, with deep breathing, and the frequency and timing of moderate exertion, with panting and overheating during last 24hours and last 2 hours preceding stroke onset. Exposure to unusual vigorous physical exertion as triggering risk factor for stroke was defined as vigorous physical exertion within one hour preceding stroke onset in subjects who exercise less than three times per week.

STATISTICAL ANALYSIS:
Data was entered into an electronic database for statistical analysis (SPSS, VERSION 20.0). Data is presented as number (%) or mean (SD) as appropriate. The results are reported as OR (95% CI). The p-value less than 0.05 is considered as statistically significant.

RESULTS
The present study was a hospital based study conducted at Dr RP Government Medical College Tanda. Out of a total of 380 patients admitted in the wards a hundred and twenty(120)patients were enrolled for the purpose of study as rest were excluded . 73 (60.8%) patients were males and the remaining 47 (39.2%) were females. Of the total 120 patients, 61 (50.8%) were between 61 – 80 years of age and 45 (37.5%) were in the age group of 41 – 60 years. Mean age of male and female patients was 62.53 ± 13.06 and 63.74 ± 14.37 years respectively.

Table 1: Association between triggers of stroke in control and hazard period

Triggers	Present 2 hours prior	Absent 2 hours prior	Total	Odds ratio (95% CI)	P value
Drug abuse					
Present 24 hours prior	3	12	15	8.5 (1.5- 46.9)	0.025
Absent 24 hours prior	3	102	105		
Total	6	114	120		
Alcohol					
Present 24 hours prior	13	19	32	1.684 (1.265 - 2.243)	0.000
Absent 24 hours prior	0	88	88		
Total	13	107	120		
Tea intake					
Present 24 hours prior	47	65	112	1.723 (1.472 - 2.017)	0.022
Absent 24 hours prior	0	8	8		
Total	47	73	120		
Fever					
Present 24 hours prior	3	6	9	1.500 (0.945 - 2.381)	0.000
Absent 24 hours prior	111	0	111		
Total	114	6	120		

Table 2: Association between triggers of stroke in control and hazard period(cont)

Smoking					
Present 24 hours prior	26	12	38	3.167(1.983-5.057)	.000
Absent 24 hours prior	0	82	82		
Total	26	94	120		
Positive emotions					
Present 24 hours prior	111	0	111	.111(.018-.705)	.000
Absent 24 hours prior	1	8	9		
Total	112	8	120		
Negative emotions					
Present 24 hours prior	0	2	2		
Absent 24 hours prior	0	118	118		.000
Total	0	120	120		
Unusual physical exertion					
Present 24 hours prior	2	4	6	.026(.003-.251)	.000
Absent 24 hours prior	1	113	114		
Total	3	117	120		
Trauma					
Present 24 hours prior	0	4	4	0.991(0.975-1.008)	1.000
Absent 24 hours prior	1	115	116		
Total	1	119	120		

Table 1 and 2 shows various triggers in our study which were assessed in control (24 hours) and hazard period (2 hours) prior to stroke in the same patient. Drug abuse as a trigger was present in 15 out of 120 patients with the odds ratio 8.5 (95% CI 1.540- 46.923) and drug abuse during 2 hours prior to stroke was present in 6 out of 120 patients . Drug abuse as a trigger 2 hours prior to stroke onset was statistically significant with a p value of 0.025.Similarly alcohol intake 2 hours prior to stroke was present in 13 out of 120 patients with the odds ratio1.684 (95% CI 1.265-2.243). Alcohol abuse as a trigger 2 hours prior to stroke onset was statistically significant with a p value of 0.000. Smoking prior 2 hours to stroke was present in 26 out of 120 patients with the odds ratio3.167 (95% CI 1.983-5.057). Smoking as trigger 2 hours prior to stroke onset was statistically significant with a p value of 0.000.

DISCUSSION

The studies on the triggers of stroke in developing countries like India at present are scanty. This study was undertaken in the department of neurology at DR RPGovernment Medical College Tanda to assess the triggers of both ischemic and haemorrhaghic stroke.

Triggers that have been widely studied in myocardial infarction, such as physical exertion, psychological factors, or sexual activity have been very little examined in ischaemic stroke.[14]

The mean age of our study population was 63.01 (±13.541 SD) years. In a study on Parallel Morning and Evening Surge in Stroke Onset, Blood Pressure, and Physical Activity by George S. Stergiou the diurnal variation of stroke onset was compared with the diurnal variation of BP, pulse rate (PR), and physical activity in 3 independent groups of Greek hypertensives 51 to 80 years of age (633 stroke patients, 379 subjects with 24-hour ambulatory BP monitoring, and 50 subjects with 24-hour physical activity monitoring through wrist devices. The mean age among stroke patients was 68.7±7.6 years.

Fever was significantly associated 2 hours prior to stroke onset with odds ratio 1.500(0.945-2.381) with p value of 0.000 in our study. Results by Bova et al are similar to our study.They are in accordance with other studies reporting that acute infection during the preceding week is more frequent among IS patients. Infections among their patients were mainly of bacterial origin. Recent studies on the possible mechanisms of infection-associated stroke revealed that there was significant elevation in peripheral blood of interleukin-1 and interleukin-6 and inhibition of polymorphonuclear activity. In a small series of stroke patients who had an associated infection, increased levels of TNF- were detected, and TNF- was suspected as a potential mediator in infection associated stroke. [15,16,17]

Drug abuse as a trigger 2 hours prior to stroke onset was statistically significant with a pvalue of 0.025in our study. Drug abuse in our study pertains to only over the counter drug intake and no other form of drug abuse. Petitti et al found a

nonsignificant association between IS and drug abuse within the preceding week (OR4.5; 95% CI, 0.9 to 21.6), whereas Qureshi et al did not find any significant association (OR1.2; 95% CI, 0.4 to 3.8). Our study was not similar to these studies.

Alcohol abuse as a trigger 2 hours prior to stroke onset was statistically significant with a p value of 0.000 in our study. Gorelick concluded that acute alcohol ingestion is not an independent risk factor for cerebral infarction in middle-aged and elderly patients. Hillbom et al concluded that intake of > 40 g ethanol within the 24 hours preceding the onset of illness increased the risk for acute brain infarction both among men (P < .001) and women (P < .01) . Significant risks were not observed in women, because the material was too small and women rarely drink for intoxication in Finland.[18]

Our study results differ from a study by jamrozik et al which concluded that Consumption of 1 to 20 g/d alcohol in the preceding week was associated with a significant reduction in the risk of all strokes, all ischemic strokes, and of primary intracerebral hemorrhage. According to study by malarcher women who drank in the past week and whose average intake for the week was <12 g of alcohol per day had an almost 60% lower stroke risk than never drinkers (OR 0.42, 95% CI 0.27 to 0.67). Women who drank 12 to 24 g/d, on average, during the past week also had a lower risk than never drinkers, but this comparison was not statistically significant (OR 0.64, 95% CI 0.27 to 1.54). [19,20,21]

Smoking as trigger 2 hours prior to stroke onset was statistically significant with a pvalue of 0.000 in our study. Relative risk of stroke following smoking was more among males (OR 3.300; 95% CI 1.967-5.536) as compared to females. The results are not comparable with any of the studies. Further research needs to be undertaken for the same.

Tea intake as trigger 2 hours prior to stroke onset was statistically significant with a p value of 0.022in our study. Worldwide, tea is the commonest beverage after water. A study from India has shown beneficial effect that tea consumption of 450 ml or more than or equal to three cups per day was associated with reduction of the incidence of recurrent ischemic stroke.[22] This is in contrast with our study. None of the patients in our study consumed coffee. This is in contrast with a study by Mostofsky , in which they found that coffee consumption was associated with a transient risk of ischemic stroke in the subsequent hour that was 2.0 times higher than the risk during periods with no coffee consumption, and the risk returned to baseline by 2 hours. The findings were consistent with 2 case crossover studies on coffee intake and other acute cardiovascular events.[23] Sexual activity did not trigger stroke in our study.This may be due to several factors, such as recall, estimation problems, shyness etc.

Positive emotions 2 hours prior were associated significantly (p value 0.000) with onset of stroke odds ratio .111 (95% CI .018-.705) in the present study. Negative emotions were also associated significantly (p value 0.000) with onset of stroke. According to a study by Koton the OR for negative emotions was 14.0 (95% CI 4.4 to 89.7),body posture in response to a startling event 24.0 (95% CI 5.1 to 428.9) . Negative emotions, anger, and sudden changes in body posture in response to a startling event appeared to be independent triggers for ischemic stroke.

There was a strong positive correlation between scores for stressful life events and negative affect (r=.61, P<.0001), which indicated that these measures were related and jointly assessed the common variable of recent psychological stress in a study by Macko et al. The negative affect score in stroke group was 4±3.9, 5.1±4.3 in community control group . There was a strong positive correlation (r=0.980) between negative emotions in last 24 hours and negative emotions in last 2 hours in our study. The score however varies between the two studies.

Trauma as trigger 2 hours prior to stroke onset was not statistically significant in our study. Lastly unusual physical exertion was associated significantly (p value 0.000) with onset of stroke OR.026 [95% CI (.003-.251)]. In this present study there was no history of trauma among females and relative risk of trauma among males 2 hours prior to stroke was 0.986 (95% CI0.958-1.014).

The relative risk of trauma 2 hours prior to stroke was more in the age group 61 and above (OR .985;95% CI .957-1.014). This may be due to age related weakness of limbs.The relative risk of stroke following unusual physical exertion 2 hours prior to stroke in age group 20-60 years was 1.305 (95% CI.740-2.301) and among 61 and above it was 2.000 (95% CI .500-7.997).

CONCLUSIONS :

It could be concluded from the present study that presence of drug abuse, alcohol abuse, smoking, tea intake , fever, positive emotions , negative emotions and unusual physical exertion two hours prior to stroke associated significantly as triggers. Trauma as a trigger was not found to be significantly associated. Coffee intake, sexual intercourse and sudden posture change were not found to trigger stroke.

Limitations :

Data in this study were collected through patients' interviews. Obviously, sudden death stroke cases and patients that did not survive the first 24 hours after the stroke (interviews were not conducted during the first 24 hours) could not be included. The study population includes stroke patients surviving the first 24 hours after the stroke.

It is possible that eligible excluded patients had more severe manifestations of stroke leading to selection bias . Patients were asked about unusual events such as exceptionally heavy physical exertion, fever, anger, sudden changes in posture in response to a startling event and sudden changes in environmental temperature. The information was easily recalled by the patients but asking about exposures during short periods immediately before the stroke onset helped minimizing recall biases.

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