Impact of Non-compliance with Antihypertensive Management on Development of Stroke among Hypertensive Patients: A Case–Control Study

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Abstract

Introduction: Hypertension and stroke are two major health problems in India. Uncontrolled hypertension increases the chances of development of stroke. The main reason for inadequate control of blood pressure is non-compliance to the treatment regimen; both pharmacological and behavioral. The aim and objective of the study were to assess the relationship between non-compliance to antihypertensive management and development of stroke. It was also aimed to identify non-compliance among patients with hypertension.

Materials and Methods: This was a one to two individually matched case–control study conducted among 139 cases and 278 controls in a tertiary care hospital of West Bengal. A self-developed validated questionnaire was used to obtain information regarding compliance from hypertensive people and patients with stroke. Antihypertensive management regimen included compliance to medication, dietary restrictions, exercise, cessation of smoking, and cessation or restriction of alcohol intake. Medication adherence was assessed using four-item questionnaires on a five-point Likert scale. A score >9 was considered as non-compliant. Other components were assessed with "Yes" or "No" questions. A total score of four out of five were considered as compliant to antihypertensive management. Descriptive statistics such as mean, percentage, and inferential statistics such as Mantel-Haenszel odds ratio (OR_{MH}) were used in this study.

Results: The mean age of cases was 51.62 (±5.1 standard deviation [SD]) and that of controls was 54.79 (±4.1 SD). Sample characteristics were equally distributed among cases and controls except for educational qualification and income. Nearly half (46%) of the sample were in the age group of 56–60 years of age. The exposure to non-compliance increases the odds of getting a stroke and was highly significant ($P < 0.05$).

Conclusion: There is a significant association between non-compliance to antihypertensive management and development of stroke. It is important to conduct an awareness program among hypertensive people regarding the importance of compliance to the treatment regimen. More consideration and care should be given to enhance the behavioral aspects of the management of hypertension to improve compliance.

Keywords: Hypertension, non-compliance, stroke

INTRODUCTION

Hypertension is the most important risk factor for worldwide morbidity and mortality and a major public health problem which affects 20% of the adult population, responsible for over 70% of stroke in women and 40% in men and the single most important persuasive threat issue for stroke.[1-4] Hypertension is one of the major mainsprings which contributes to disability, health care costs, and stroke mortality[5,6] and one of the major but preventable or controllable risk factors for stroke. Low adherence to antihypertensive therapy is found to be associated with uncontrollable hypertension.[7] The most common neurological disease "Stroke" is not a medical jargon for the layman in the present scenario. Being the second cause of death due to non-communicable disease, stroke is a major health problem in many countries.[8-10] Stroke, a feasible outcome of hypertension, often leads to death and

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disability.[11-13] The echelon of disability varies from patient to patient according to the type of stroke suffered, the part of the brain affected, and the size of the damaged area. In developing countries, stroke remains a prime public health problem. Stroke, also called brain attack, occurs when the blood flow to an area of the brain is interrupted, resulting in some degree of permanent neurological damage.[14]

It occurs when part of the brain does not receive the needed blood flow for one of two reasons either the blood supply to part of the brain is suddenly interrupted, or because a blood vessel in the brain ruptures and blood invades the surrounding areas. Without the blood supply, the brain cells start to die (cerebral infarction), leading to brain damage. Approximately two million brain cells die every minute during a stroke, which increases the risk of brain damage, disability, and death. Stroke is the third leading cause of death in the United States and the UK after heart disease and cancer, and the number one cause of adult disability.[15] Many studies conducted at the UK and the Netherlands showed that quality control of hypertension is strongly related to the occurrence of stroke.[16-18] Even though both systolic and diastolic hypertensions are associated with increased risk for the stroke, systolic blood pressure (BP) is found to be more dangerous for developing the cerebrovascular disease.[19] Clinical trials show that antihypertensive therapy is strongly associated with 35–45% mean reduction in stroke incidence.[20] This antihypertensive treatment can be pharmacological or non-pharmacological.

Thus, the aim of the present study was to assess whether individuals with low adherence to antihypertensive management are at risk of developing stroke.

MATERIALS AND METHODS

Research design
This study adopted a quantitative approach using case–control retrospective study design. The subjects were divided into cases and control as per sample selection criteria. It was conducted among 139 patients diagnosed to have a stroke and was admitted in a multidisciplinary tertiary care teaching and referral hospital in West Bengal affiliated to West Bengal University of Health Sciences over a period of 6 months from March to August 2016.

The sample size was calculated for an estimated OR of two and expecting a 20% exposure among controls with 90% power and 5% one-sided alpha (α) risk. The case to control ratio was two. The calculated sample size for case was 139. Consecutive sampling technique was used to collect cases. To detect small differences between two groups and to compensate the potential loss of controls, it was decided to select one to two matched controls from the same settings. Hence, 278 hypertensive patients were recruited as controls that were attending outpatient department (OPD) from the same setting and were individually matched.

The cases and controls were individually matched by age (±2 years), sex, starting point of medication, time of diagnosis of hypertension, enrolment location, residential status, and use of complementary and alternative medicine.

Sample selection criteria for cases
The patients irrespective of sex and aged 40–60 years, and admitted (≥3 days) in acute ward/ICU with a physician made diagnosis of 1st time stroke, and a computed tomography head finding suggestive of ischemic or hemorrhagic stroke and with a history of hypertension only on antihypertensive treatment for >1 year were included in the study. The age group was restricted up to 60 years as a stroke below this age is preventable.[21]

Sample selection criteria for controls
Hypertensive patients with no other comorbidities or any history of stroke or stroke-like symptoms and on antihypertensive treatment for >1 year duration attending medical OPD of same tertiary care hospital.

Exclusion criteria
Patients with any systemic diseases other than hypertension and do not have a recorded BP reading on their medical
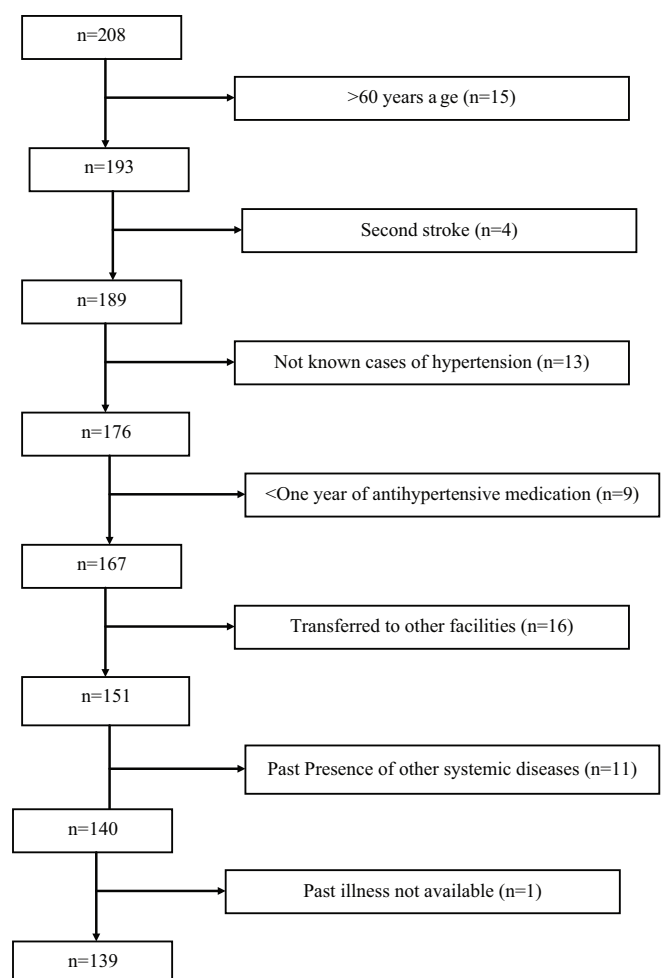
Figure 1: Patients flow into the study

record or diary. Patients who are not able to give consent or not able to obtain consent from a proxy respondent and those who participated in the pilot study were excluded from the study. Proxy respondents in this study meant either spouse or a first degree relative living in the same home and were aware about patients' past health status including medication history.

A total of 214 patients with stroke were admitted from March to August 2016, and 75 cases were excluded due to various reasons, as shown in the flow chart [Figure 1].

Tool development

A self-developed structured questionnaire was used to collect socio-demographic data and compliance status. The first part of the questionnaire dealt with personal information such as age, gender, marital status, education, occupation, monthly income, and body mass index.

The second part consisted of a questionnaire to assess the compliance level to antihypertensive management. Compliance to five components of antihypertensive management regimen was assessed separately using a questionnaire adopted from various literature.

a. Medication adherence was assessed using a four-item questionnaire on a five-point Likert scale ranging from 0 to 4. A score >9 was considered as non-compliant
b. Adherence to dietary restrictions was assessed using "Yes" or "No" questions. Dietary restrictions in this study mean following dietary assistance to stop hypertension
c. Adherence to modification of alcohol intake was assessed using "Yes" or "No" questions. Alcohol intake was categorized in to never/former drinker and current drinker
d. Adherence to exercise was assessed using "Yes" or "No" questions. Patients were categorized as physically active if they were involved in moderate to strenuous exercises at least 3 days/week or progressively inactive
e. Adherence to the cessation of smoking was assessed with "Yes" or "No" questions. Smoking status was defined as never, former, or current smoker. Current smokers were individuals who smoked any tobacco in the past 12 months and included those who had quit within the past 1 year. Former smokers were defined as those who had quit more than a year earlier.

A well informed written consent was taken either from patients or from the proxy respondent. Institutional Ethical Clearance was obtained before data collection.

Data were collected over a period of 6 months. The information was collected either from the patient or a proxy respondent in cases group and from patients in the control group. Even though stress management is an important component of antihypertensive management regimen, it was not included in this study as stress is highly subjective and in some cases, proxy respondents were the informers. In the setting where the study was conducted, all hypertensive patients were asked to maintain a diary or a notebook at the time of registration.

An identification mark was placed on the diary or notebook of pilot study sample so as to identify and exclude them from the main study.

Statistical analysis

Differential statistics such as mean and percentage were calculated for demographic data and compliance level. The relationship of non-compliance to antihypertensive management and occurrence of stroke was carried out using matched Mantel-Haenszel odds ratio (OR_{MH}). This was used to control the confounding effect as the controls are not selected randomly but selected according to matching criteria. Hence, to control the superimposed confounding factors, we used a stratified analysis. The matched odds ratio is calculated using pairs instead of individuals, and a pair is considered as a

Table 1a: Demographic characteristics

Variables	Case (n=139)	Control (n=278)
	n (%)	n (%)
Age (years)		
41–45	6 (4)	13 (5)
46–50	14 (10)	30 (11)
51–55	55 (40)	107 (38)
56–60	64 (46)	128 (46)
Gender		
Male	124 (89)	248 (89)
Female	15 (11)	30 (11)
Marital status		
Married	116 (83)	234 (84)
Single	2	-
Cohabitant	-	-
Widow/widower/divorce	21 (15)	44 (16)
Level of education		
No formal education	6 (4)	11 (4)
Primary	23 (17)	60 (21)
Secondary	64 (46)	122 (44)
Higher secondary	16 (11)	19 (07)
Diploma/degree	22 (16)	49 (18)
Others	8 (6)	17 (6)
Occupation		
Skilled	114 (82)	218 (78)
Unskilled	9 (6)	11 (4)
Professional	16 (12)	49 (18)
Income (Rs)		
<5000/month	-	-
5001–10,000	3 (2)	-
10,001–15,000	40 (29)	56 (20)
>15,000	96 (69)	222 (80)
Residence		
Urban	69 (50)	150 (54)
Rural	70 (50)	128 (46)
BMI (kg/m²)		
Normal	33 (24)	85 (30)
Overweight	79 (57)	144 (52)
Obese	27 (19)	49 (18)
Family h/o stroke		
Yes	91 (65)	118 (42)
No	48 (35)	160 (58)
Blood pressure		
Normotensive	5 (4)	158 (57)
Hypertensive	39 (28)	84 (30)
Hypotensive	95 (68)	36 (13)
Cholesterol level		
Normal	19 (14)	203 (73)
Hypercholesterolemia	120 (86)	75 (27)

stratum. In this study, we had six strata – two concordant and four discordant strata.

RESULTS

The collected data were tabulated, analyzed, and interpreted.

Demographic characteristics

Table 1a shows the distribution of cases and controls according to their demographic characteristics.

Table 1a-c show the distribution of cases and controls according to demographic characteristics. As it was an individually matched case–control study, sample characteristics were equally distributed among cases and controls except for educational qualification and income. Nearly half (46%) of the sample were in the age group of 56–60 years of age. The mean age of cases was 51.62 (±5.1 SD) and that of controls was 54.79 (±4.1SD).

The relationship between non-compliance to antihypertensive management and risk for development of stroke is shown in Table 2. In this study, the OR_{MH} explains that the exposure to non-compliance increases the odds of getting stroke and is highly significant; thus, the null hypothesis $OR_{MH} = 1$ is rejected. Table 2 illustrates the compliance pattern to antihypertensive management in total and compliance to five components separately. Even though there were four types of discordant pairs, for computing the odds ratio it is made into two discordant data as shown below.

The discordant pairs are:
1. Case compliant and both controls non-compliant
2. Case compliant and one control are non-compliant
3. Case non-compliant and both control compliant
4. Case non-compliant and one control compliant.

This was combined and formed to:
a. Case compliant and control non- compliant
b. Case non-compliant and control compliant.

Table 1b: Sample characteristics

Variables	Case (*n*=139)	Control (*n*=278)
	n (%)	*n* (%)
Duration of hypertension (years)		
1–3	28 (20)	56 (20)
3.1–5	35 (25)	70 (25)
>5	76 (55)	152 (55)
Use of CAM		
Yes	59 (42)	118 (42)
No	80 (58)	160 (58)
Experience stress		
Yes	86 (62)	190 (68)
No	53 (38)	88 (32)

Table 1c: Mean age of the sample

S. No.	Sample	Frequency (*n*)	Mean (years)	SD
1.	Case	139	51.62	5.1
2.	Control	278	54.79	4.1

DISCUSSION

There are many epidemiological and clinical studies proved the continuous and direct relationship that exists between hypertension and stroke.[22] Studies showed that there was a significant association between non-compliance to antihypertensive management and stroke.[23-25] The present individually matched case–control study assessed the relationship between non-compliance to antihypertensive management and stroke. The objective of the study was to assess the relation between non-compliance to antihypertensive management and the development of stroke. The results of the study revealed a strong relationship between non-compliance to antihypertensive management and stroke.

According to demographic characteristics studied

Nearly half (46%) of the participants were in the age group of 56–60 years. Approximately 90% of the participants were male and the majority (83%) were married. Secondary education was the highest level of education among 46% of the sample and most (82%) were skilled workers. Residential status was almost similar among cases and controls. More than half (57%) had overweight. Among cases, 65% had a family history of the stroke whereas 58% of controls did not have a family history of stroke. Most (86%) of the cases had hypercholesterolemia. This supports the fact that those having a family history of stroke and having a high level of cholesterol have a greater risk for stroke.[26,27]

The study shows that exposure to non-compliance to antihypertensive management regimen increases the odds of developing stroke and was statistically significant (MH $_{OR}$ 2.8462, $P < 0.000$). Medication non-adherence (taking <80% of the number of prescribed pills) occurs in about 50% of newly treated hypertensive patients within the 1st year of treatment and has been identified as the main cause of uncontrolled hypertension. Non-adherence increases the risk of uncontrolled hypertension about 5 times, as well as overall mortality, hospitalization rate, and cost of care.[28]

The impact of non-adherence is likely mediated through uncontrolled hypertension, which is known to increase the risk of stroke.[18] It was observed that uncontrolled BP among treated hypertensive patients was moderately associated with ischemic stroke (risk ratio = 1.5 [95% confidence interval (CI), 1.2–1.9]) and strongly related to hemorrhagic stroke (risk ratio = 3.0 [95% CI, 1.7–5.4]). Our findings are also consistent with Xu *et al*. They found that 20% increment in antihypertensive medications adherence level was associated with a 9% lower risk of stroke (RR, 0.91; 95% CI, 0.86–0.96).[29]

The current study finding revealed that non-compliance to medication increased the odds of developing stroke and was highly significant (MH $_{OR}$ 3.4091, $P < 0.000$). Herttua *et al*. observed that in hypercholesterolemia patients with hypertension, relative to those who adhered to statins and antihypertensive therapy, the odds ratio at the year of stroke death was 7.43 (95% CI: 5.22–10.59) for those nonadherent both to statin and antihypertensive therapy, 1.82 (95% CI:

Table 2: Relationship between non-compliance and risk for stroke (*n*=139 pairs)

S. No.	Characteristics	F	Discordant pairs (*n*)	OR$_{MH}$	95% CI		*P* value	McNe mar value
					Lower limit	Upper limit		
1.	Compliance to antihypertensive management regimen							
	Case and control compliant	32	100	2.8462	1.8205	4.456	<0.0001	23.040
	Case and control non-compliant	7						
	Case compliant, control non-compliant	26						
	Case non-compliant, control compliant	74						
2.	Compliance to medication							
	Case and control compliant	40	99	3.4091	2.1196	5.4831	<0.0001	28.9588
	Case and control non-compliant	2						
	Case compliant, control non-compliant	22						
	Case non-compliant, control compliant	75						
3.	Compliance to diet							
	Case and control compliant	25	111	2.0556	1.3803	3.0612	<0.0001	13.1273
	Case and control non-compliant	4						
	Case compliant, control non-compliant	36						
	Case non-compliant, control compliant	75						
4.	Compliance to exercise							
	Case and control compliant	23	108	3.1538	2.0289	4.9026	<0.0001	29.037
	Case and control non-compliant	8						
	Case compliant, control non-compliant	26						
	Case non-compliant, control compliant	82						
5.	Compliance to alcohol							
	Case and control compliant	30	108	2.6	1.7065	3.9614	<0.0001	21.3333
	Case and control non-compliant	1						
	Case compliant, control non-compliant	30						
	Case non-compliant, control compliant	78						
6.	Compliance to smoking							
	Case and control compliant	27	106	4.0476	2.5105	6.5258	<0.0001	38.6415
	Case and control non-compliant	6						
	Case compliant, control non-compliant	21						
	Case non-compliant, control compliant	85						

a. McNemar test is used as the number of discordant pairs are >20. OR$_{MH}$: Mantel-Haenszel odds ratio, CI: Confidence interval

1.43–2.33) for those non-adherent to statin but adherent to antihypertensive therapy, and 1.30 (95% CI: 0.53–3.20) for those adherent to statin, but nonadherent to antihypertensive, therapy.[30]

Our study provides vital information on the importance of adherence to dietary modifications. Non-compliance to dietary modifications increases the odds of developing stroke twice among hypertensive people than those who follow the dietary modifications (MH $_{OR}$ 2.0556, *P* < 0.000). Studies have shown that hypertensive people taking excessive salt and high fat in their diet are at risk of developing stroke.[27,31]

Regular planned physical activity or exercises reduce the risk factor for stroke by maintaining desirable BP level and reduce cholesterol level, triglycerides, and high blood sugar level.[31,32] Our study finding is in agreement with this. Non-compliance to physical activity increases the risk for stroke 3 times among patients with hypertension (MH$_{OR}$ 3.1538, $P < 0.000$). Many studies have shown that compliance to alcohol restrictions reduces the risk for stroke significantly and present study report that non-compliance to alcohol restrictions doubles the odds of developing stroke among hypertensive people (MH$_{OR}$ 2.60, $P < 0.000$) (31,33). Our study finding support the fact that risk of stroke is significantly associated with the habit of smoking (MH$_{OR}$ 4.0476, $P < 0.000$).[32-34]

Strength and limitations

Use of OR$_{MH}$ is the strength of our study as it controls the confounding effect if any was introduced during sample selection as it was a matched design.

Case–control studies are prone to recall bias and are a limitation of this type of studies. Second, the use of proxy respondent might have caused some error in producing accurate information. Third compliance with stress management was not assessed.

Conclusion

As hypertension is a major public health problem which needs early detection, awareness and control so that its improved detection and management can prevent strokes and heart attacks. There was a significant association between non-compliance to antihypertensive management and development of stroke. It is important to conduct an awareness program among hypertensive people regarding the importance of compliance with the treatment regimen. More consideration and care should be given to enhance the behavioral aspects of the management of hypertension to improve compliance.

Conflict of Interest

Authors disclaim any conflicts of interest.

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