

Poor adherence with ACE inhibitors is a risk factor of CVA with oral hypoglycemic agents in diabetic patients

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Abstract: Poor adherence with medicine declines the clinical outcome of pharmacotherapy. It may carry serious sequelae especially in case of antihypertensive drugs like cerebrovascular accident (CVA). This study has been planned to find the association of poor adherence with anti-hypertensive with CVA in diabetic and non-diabetic patients. One hundred CVA patients who were admitted through Emergency in Abbasi Shaheed hospital, a tertiary care hospital in Karachi, were recruited from Jun 2013 till Dec 2013. The criteria of inclusion was, diagnosed case of CVA, with primary hypertension, availability of patient's therapeutic record, consent of the patient or legal successor/heir. The criteria of exclusion was, secondary hypertension, newly diagnosed primary hypertensive patients and complete adherence with medication. Morisky medication adherence scale was applied. Therapeutic record was accessed. The mean age was 62.15 years with 3:1 male to female ratio. Adherence to medicine was graded <6. Patients with hypertension were 41 and with diabetes and hypertension were 59. Majority of patients were on monotherapy as compared to polytherapy (62% versus 38%). The mode of therapy was significantly different ($P < 0.05$) in the two groups. ACE Inhibitors, Calcium Channel Blockers, Beta Blockers and other agents were used by 45.16%, 35.48%, 16.12% and 03.24% patients respectively. The aforementioned drugs were used by 57.14%, 33.33% and 09.52% respectively in 21 patients who were on anti-hypertensive and oral hypoglycemic agents. A statistical significant difference ($P < 0.05$) was seen in the case of ACE Inhibitors. Similarly they were used by 42.10%, 39.47% and 18.42% in 38 patients respectively, who were on anti-hypertensive and insulin. No statistical significant difference ($P > 0.05$) was seen in any combination ($p > 0.05$). Thus it is concluded that poor adherence with ACE inhibitors may be a risk factor of CVA in diabetic patients using oral hypoglycemic agents.

Keywords: Poor adherence, Cerebrovascular accident, ACE inhibitors.

INTRODUCTION

Clinical outcome of pharmacotherapy is declined by poor adherence to medicines (Gatwood *et al* 2014) especially in cardiovascular diseases (Rajpura and Nayak 2014). It increases health care cost (Sokol 2005, Summaria *et al* 2013) by increasing number of medications and seriously undermining the benefits of present medical care (Gatwood *et al.*, 2014). It is a major contributor in worsening of disease even death (Ho *et al.*, 2006). This study has been planned to find the association of poor adherence with anti-hypertensive with cerebrovascular accident (CVA) in diabetic and non-diabetic patients.

MATERIALS AND METHODS

The study was conducted after approval of institutional board (Ref; AS 312/19/qf; dated April 28, 2013). CVA patients who were admitted in the ward through emergency in Abbasi Shaheed hospital, a tertiary care hospital in Karachi, were recruited from June 2013 till Dec 2013. The recruitment was continued in date bracket

till 100 patients agreed to participate in our research. The criteria of inclusion was, the diagnosed case of CVA with a history of primary hypertension, availability of patient's therapeutic record, presence of concierge intimate if the patient is unable to provide information about medicine adherence and consent from the patient or legal successor /heir for an unconscious patient. The criteria of exclusion was, secondary hypertension, newly diagnosed primary hypertensive patients who were not receiving any anti-hypertensive therapy or were on anti-hypertensive treatment since less than 3 months and complete adherence as per Morisky medication adherence scale (Morisky *et al.*, 2008) to antihypertensive treatment. A structured interview for the assessment of medication adherence was taken. Morisky medication adherence scale was applied. Therapeutic record was accessed after permission from concern authorities.

STATISTICAL ANALYSIS

Data entry and analysis was performed using Superior Performance Statistical Software (SPSS) version 20. Data was presented as mean \pm SEM with 95% confidence interval. One way ANOVA followed by post hoc was

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performed for comparison of values with control. Values of $P \leq 0.05$ were considered statistically significant and $p \leq 0.005$ as highly significant.

RESULTS

Table 1: shows that 100 recruited CVA patients who had the mean age of 62.15 years and were in 3:1 male to female ratio. They were diagnosed on history, physical examination and CT/MRI Scan. They were all irregular user of antihypertensive drugs and were graded <6 on Morisky scale.

Table 2: Shows underlying diseases like hypertension and diabetes. Out of 100 recruited patients with hypertension were 41 and with diabetes and hypertension were 59.

Table 3: Represents mode of therapy. Patients on monotherapy were 62% and on poly therapy were 38%. The mode of therapy was significantly different ($P < 0.05$) in the two groups.

Table 4: shows relative use of different groups of antihypertensive drugs in the patients receiving monotherapy. ACE Inhibitors, Calcium Channel Blockers, Beta Blockers and Other agents were used by 45.16%, 35.48%, 16.12% and 03.24% respectively.

Table 5: shows association of combination of antihypoglycemic and antihypertensive drugs, with CVA. Table 5 A represents that ACE Inhibitors, Calcium Channel Blockers and Beta Blockers were used by 57.14%, 33.33% and 09.52% of 21 patients respectively, who were on anti-hypertensive as well as oral hypoglycemic agents. Statistically significant difference ($p < 0.05$) was observed in the case of ACE Inhibitors.

Table 5 B shows that ACE Inhibitors, Calcium Channel Blockers and Beta Blockers were used by 42.10%, 39.47% and 18.42% respectively in 38 patients who were on anti-hypertensive and Insulin. No statistical significant difference ($P > 0.05$) is seen in any combination.

Two patients who were on antihypertensive agents other than ACE Inhibitors, Calcium Channel Blockers and Beta Blockers and one patient who was using some homeopathic medicine as antidiabetic agent was not included in table 5 A & B.

DISCUSSION

The studies on the prevalence of hypertension show an alarming rise in the number of hypertensive patients and it has been estimated that there will be 1.56 billion hypertensive patients in the beginning of next decade (Kearney 2005) with a ratio of 1:2 in economically developed and developing countries. Stroke is an

important fatal sequela of this disease (Lackland 2013) and will be one of the leading causes of death and disability in future (Shah 2006). Therefore hypertension requires acme consideration. The data base of PUBMED, MEDLINE, EMBASE, OVID, CNKI, MEDCH and WANFANG from January 1, 1996 to July 31, 2012 on a total of 177 reports having 31 Randomized Clinical Trials with 273543 participants shows that Calcium Channel Blockers, Beta-adrenergic Blockers, Angiotensin Converting Enzyme Inhibitors and Diuretics are exclusively used for the treatment of hypertension (Chen and Yang 2013) and to reduce the risk of stroke. Majority of the patients require two or more medicines to achieve desired blood pressures (Moser 2004). Intensive reductions in blood pressure produce larger reduction in the risk of major cardiovascular events (Wang *et al* 2005). Our study shows that large proportion of our CVA patients were using monotherapy as compared to multidrug treatment. Therefore we consider that use of combination of antihypertensive drugs simultaneously reduces the risk of fatal cardiovascular events relatively as compared to the use of only one antihypertensive drug. This is especially true for old age patients (the main population of our study), and it has been supported by a number of studies (Amery *et al* 1985, Beckett *et al* 2008, Aronow 2012). Unfortunately the drug adherence in patients with hypertension is very low (Morisky *et al* 2008, Krousel-Wood *et al* 2010, Tulner *et al* 2010, Wiliński and Dabrowski 2013). Sudden discontinuation of antihypertensive leads to hypertensive emergencies (Karachalios *et al* 2005). Our results indirectly show that rebound hypertension is more grievous in patients using single drug than multi drug antihypertensive therapy. It is possible because combination of drugs can cause less serious withdrawal due to different rates of absorption, half-lives, different rates of conversion into active or inactive metabolites and excretion. Drug interaction may also be one of the factors. However further research is needed on this subject (van der Cammen *et al* 2014). Rebound hypertension to levels higher than those that existed before treatment has been noted with discontinuation of beta adrenergic receptor antagonists in hypertensive patients (Houston and Hodge 1988) but the phenomenon may occur after discontinuation of any of a variety of drugs (Hubbell and Weber 1980). This can be true in case of ACE Inhibitors too. Elevated Plasma renin has been found as a result of inhibition of both short and long loop negative feedback on renin release after use of ACE inhibitors (Jackson 2001a) which renders patients hyper responsive to ACE inhibitor withdrawal. Baroreceptor function and cardiovascular reflexes are not compromised and responses to postural changes and exercise are impaired a little with ACE inhibitors (Jackson 2001b) which may also be a participant in rebound hypertension. Although higher frequency of this phenomenon, in patients who abruptly withdrew ACE inhibitors, is not supported by many other studies (Garbus

Table 1: Characteristics of the patients

Variable	Description.
Total number of Cases	100
Mean Age (Range)	62.15(52-73) years.
Male: Female ratio.	3:1
Criteria for the diagnosis of CVA	History, Physical Examination and CT/MRI Scan.
Morisky Scale	<06

Table 2: Underlying disease

Underlying Disease	No. of Patients (Total Patients)	Percentage
Hypertension	41	41
Diabetes Mellitus and hypertension.	59	59

Table 3: Mode of antihypertensive therapy

Mode	No. of Patients(Total Patients)	Percentage	Significance
Mono therapy	62(100)	62	<0.05
Poly therapy	38(100)	38	

Table 4: Antihypertensive drugs used in 62 CVA patients receiving monotherapy for hypertension

Antihypertensive agent	Number of Patients	Percentage
ACE Inhibitors	28	45.16
Calcium Channel Blockers	22	35.48
Beta Blockers	10	16.12
Other Agents	02	03.24

Table 5: Association of hypoglycemic and antihypertensive drugs with cva.

A) Antihypertensive and Oral Hypoglycemic Agents in 21 patients

Antihypertensive agent	Number of Patients	Percentage	Significance
ACE Inhibitors	12	57.14	.032
Calcium Channel Blockers	07	33.33	.227
Beta Blockers	02	09.52	.200

B) Antihypertensive and Insulin in 38 patients

Antihypertensive agent	Number of Patients	Percentage	Significance
ACE Inhibitors	16	42.10	.214
Calcium Channel Blockers	15	39.47	.491
Beta Blockers	07	18.42	.463

et al., 1979), Hubbell and Weber 1980, Karachalios et al., 2005). But it may be possible if CVA is the end point of outcome because role of renin and related mediators has been established in studies on regulation of blood pressure in brain (Zhao et al., 2001, Huang et al., 2010, Leenen 2010) and hypersensitivity of Cerebral vasculature to these mediators has also been established due to genetic susceptibility (Lebrun et al., 1996).

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