

Changing chronobiology of cardiovascular outcome following prophylaxis

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ABSTRACT

Cardiovascular events like angina, myocardial infarction and stroke have shown an increasing occurrence in the morning hours. We did this pilot nested case control study to see for any change in the time pattern of occurrence of cardiovascular events among patients on prophylaxis. A pilot study was done and the demographic characters, history of cardiovascular diseases, time of occurrence of cardiovascular event, history of drug intake and compliance were noted. Eighty four patients on prophylaxis and 135 patients presenting for the first time reported during the study period. Age did not show any significant difference. More males were getting prophylaxis for stroke and for the combined cardiovascular events. Time distribution of events showed peak occurrence between 8 to 12 hr followed by 20 to 24 hr among those who were not on prophylaxis and reverse in those on secondary prophylaxis. Odds of developing cardiovascular events though was not significantly different, was higher between 16-20 hr (1.26), 20-24hr (1.48) and 0-4 hr (1.22) among those on prophylaxis. Seventy eight patients were taking antihypertensives. This observation demands further studies to determine the cause of evening increase in cardiovascular event especially since very little is known regarding evening exaggeration of risk factors which is becoming relevant especially in those getting prophylaxis.

Keywords: Chronobiology, cardiovascular outcome, prophylaxis.

INTRODUCTION

Studies have shown that cardiovascular events like angina, myocardial infarction and stroke are more common during the morning hours with a probable second peaking towards evening.¹⁻¹¹ Patients who are on prophylaxis of these diseases are expected to have an altered pattern due to variation of the physiological parameters by drugs and life style modifications. Very few studies have been done with this objective and those studies have observed a blunting of morning peak of cardiovascular outcome.^{1,12-18} Since we have observed a different pattern, we did this pilot study to compare the time of occurrence of cardiovascular events like myocardial infarction, angina and stroke among patients on prophylaxis with drugs with those who are not on prophylaxis.

MATERIALS AND METHODS

This was a pilot nested case control study conducted at the emergency department of an Indian tertiary care hospital from October 2004. Patients of either sex who reported to the emergency department with suggestive history, signs and symptoms, electrocardiograph evidence of angina or myocardial infarction and computerized tomography evidence of cerebrovascular disease were included in the study. Patients or their bystanders were interviewed regarding demographic characters, history of cardiovascular diseases, time of occurrence of cardiovascular event, history of drug intake and compliance. Exclusion criteria included patients who gave insufficient information and those taking medicines irregularly while those taking no drugs at all for the last week were considered as not on prophylaxis.

There were two groups of patients in the study, those on prophylaxis and those who presented for the first time. Each of this group had three subgroups which included angina, myocardial infarction and stroke patients. This pilot study was continued till each of these subgroups had a minimum of 25 patients. Time of occurrence of cardiovascular events were pooled to 4 hr groups and compared. Unpaired student's t test, Chi square test or Fishers exact test and odds ratio with 95.0% confidence interval by Woolf's approximation were used for analysis and 'p' value of less than 0.05 was considered significant.

RESULTS

Eighty four patients on prophylaxis and 135 patients presenting for the first time in the emergency department with angina, myocardial infarction or stroke suited our study while 17 patients gave inadequate details and had to be excluded. Age did not show any significant difference while significantly more male patients were getting prophylaxis for stroke and for the combined cardiovascular events. Time distribution of events showed peak occurrence between 8hr and 12hr followed by 20hr and 24hr among those who were not on prophylaxis and reverse in those on prophylaxis (Table-1:). Odds of developing cardiovascular events though was not significantly different, was higher between 16hr and 4hr among those on prophylaxis compared to those who were not (Fig. 1.). Seventy eight patients were taking different types of antihypertensive medications (Table-2.)

DISCUSSION

Most patients who reported to the hospital following cardiovascular event were not on prophylaxis. This stresses the importance of primary prevention to decrease occurrence of similar events. Mean age of 59 is an evidence of the tendency of lowering of age for developing cardiovascular events probably due to unhealthy life style adopted by the present generation or consumption of cyclooxygenase-2 specific inhibitors.¹⁹ Male preponderance was noted for angina, female preponderance was noted for infarction, where as 59.0% stroke patients getting prophylaxis were males while 93.0% who were not getting prophylaxis were females. On the whole, patients who were not on prophylaxis were mostly females and those on prophylaxis were equal.

There was peaking of cardiovascular outcome during early morning hours and a second peaking towards night among those not on prophylaxes. Studies have shown that myocardial infarction, angina and stroke is highest during the morning hours.^{1-3,5,6} Morning peaking has been described to be due to concurrence of risk factors for cardiovascular outcome like increase in blood viscosity,²⁰ increase in platelet aggregability,²¹ decrease in tissue-type plasminogen activator activity²², increase in catecholamine levels,²³ increase in plasma corticosteroid levels,²⁴ high blood pressure,^{20,25} high heart rate,²⁰ increased coronary vascular tone,²⁶ exaggerated morning tone of the dysfunctional endothelium,²⁷ increase in physical activity following waking up²⁸ and increase in sympathetic activity²⁶ - all these factors triggered by stress.²⁹

Bimodal distribution pattern was observed in some studies^{1,4,7-11} though unimodal was observed in others and meta-analyses.^{5,6} Beta blockers^{12-14,18} like metoprolol,^{12,18} atenolol,¹³⁻⁴ betaxolol,¹³ combination of atenolol with amlodipine,¹⁶ controlled onset extended release verapamil (COER verapamil),^{26,27} nifedipine gastrointestinal therapeutic system (NGTS),²⁶ quinapril¹² and aspirin¹⁷ have shown suppression of morning increase in cardiovascular events in various studies. Too much suppression of blood pressure in the night have shown to lead to ischemic cerebrovascular accidents.³⁰⁻³¹ Hence modulation of blood pressure has to be done with caution. Individual drug effect could not be determined because of the need to use multiple drugs.

Among patients on prophylaxis, morning incidence of cardiovascular events was lower while at evening was higher as compared to those who are not. There is a tendency for risk factors to coincide towards evening which is exaggerated both absolutely and relatively, among those on prophylaxis. Single morning intake of antihypertensives which probably takes time to take effect, and exposes the patients to higher blood pressure for initial few hours of the day may be a reason for the still high morning occurrence of cardiovascular events. Earlier studies have shown use of aspirin,¹⁷ beta blockers,¹⁸ inclusion of patients more than 70 years, smokers, diabetics, women, congestive cardiac failure patients

and those having non Q wave infarction, showing characteristic evening peak of cardiovascular outcome.¹⁸ Small sample size, customs in certain countries, difference in populations with respect to patients with various modifying factors are some of the other reasons mentioned for bimodal distribution.¹⁸ In the morning and evening a higher thrombolytic activity has been observed though in between these timings, there was least activity.³² Probably this is one of the reasons for bimodal distribution. Further studies need to be conducted to determine the cause of evening increase in cardiovascular event especially because morning peaking has been well studied and preventive measures are at least partly known while very little is known regarding evening exaggeration of risk factors which is becoming relevant especially in those getting prophylaxis.

From 4hr to 16hr, patients who were on prophylaxis for cardiovascular disease had lower odds of having cardiovascular outcome than those who were not on prophylaxis- a tendency which reversed beyond this period. This altered pattern has not been described before. Patients who are on prophylaxis can expect better care since usually these periods of higher risk are beyond working hours making it highly likely to get noticed and to get quicker care. Better control of morning blood pressure explains this observation, partly.

Inclusion of patients with stable angina, acute coronary syndromes and different types of cerebrovascular accidents together as cardiovascular events, though could have biased our study, earlier studies have shown all the above diseases to have a similar diurnal pattern.¹⁻⁶ Multiple drugs were taken by patients and each drug would have its own effect in lowering the morning risk but why there is exaggerated risk in the evening is not known. Considering the impractically long period required, if patients with similar treatment in a community set up alone are to be included, this was not attempted. A study of the above type could give a better picture of the reason behind the peculiar altered pattern of cardiovascular outcome observed. Small sample size can be a criticism but similarity of occurrence of cardiovascular outcome in the two groups makes this less relevant.

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Table-1: Demographic characteristics and pattern of patient distribution with outcome.

	Total		Angina		Myocardial infarction		Stroke		
	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated	
No: of patients	135	84	32	27	47	25	56	32	
Average age (Mean±SD)	59±12	59±12	58±11	58±11	59±10	59±14	59±14	59±10	
Age range	18-90	30-84	18-80	38-84	30-90	39-80	27-85	30-81	
Male gender (%)	42 (31)	42 (50)**	19 (59)	19 (70)	19 (40)	4 (16)	4 (7)	19 (59)***	
Outcome at various time									
	0-4	8 (6)	6 (7)	4 (13)	1 (4)	4 (9)	1 (4)	0 (0)	4 (13)
	4-8	17 (13)	5 (6)	4 (13)	2 (7)	5 (11)	2 (8)	8 (14)	1 (3)
(0-24 scale)	8-12	41 (30)	20 (24)	13 (41)	5 (19)	9 (19)	6 (24)	19 (34)	9 (28)
	12-16	15 (11)	10 (12)	1 (3)	7 (26)	6 (13)	3 (12)	8 (14)	0 (0)
	16-20	24 (18)	18 (21)	4 (13)	3 (11)	10 (21)	7 (28)	10 (18)	8 (25)
	20-24	30 (22)	25 (30)	6 (19)	9 (33)	13 (28)	6 (24)	11 (20)	10 (31)

P<0.05, * P<0.001 compared to untreated group.

Table-2: Pattern of prophylactic use of drugs by patients.

Drugs used	Time on 0 to 24 scale				Drug intake frequency			No:
	<11	11-15	15-19	>19	OD	BD	TID	
Antihypertensive drugs								113
Beta blockers	29	1	0	19	23	13	0	36
ACE Inhibitors	23	0	0	17	26	7	0	33
Calcium channel blockers	26	1	1	12	23	7	1	31
Diuretics	5	0	1	1	5	1	0	6
Angiotensin II antagonists	4	0	0	2	2	2	0	4
Alpha blockers	1	0	0	2	3	0	0	3
Antiplatelet drugs	32	2	1	13	48	0	0	48
HMG CoA inhibitors	3	0	0	23	26	0	0	26
Other CVS drugs								27
Nitrates and Nitrites	16	0	4	12	4	14	0	18
Nicorandil	3	0	0	3	0	3	0	3
Amiodorone	2	0	0	3	1	2	0	3
Warfarin	1	0	0	1	2	0	0	2
Levocarnitine	1	0	0	1	1	0	0	1
Total number of drugs	146	4	7	109	164	49	1	214

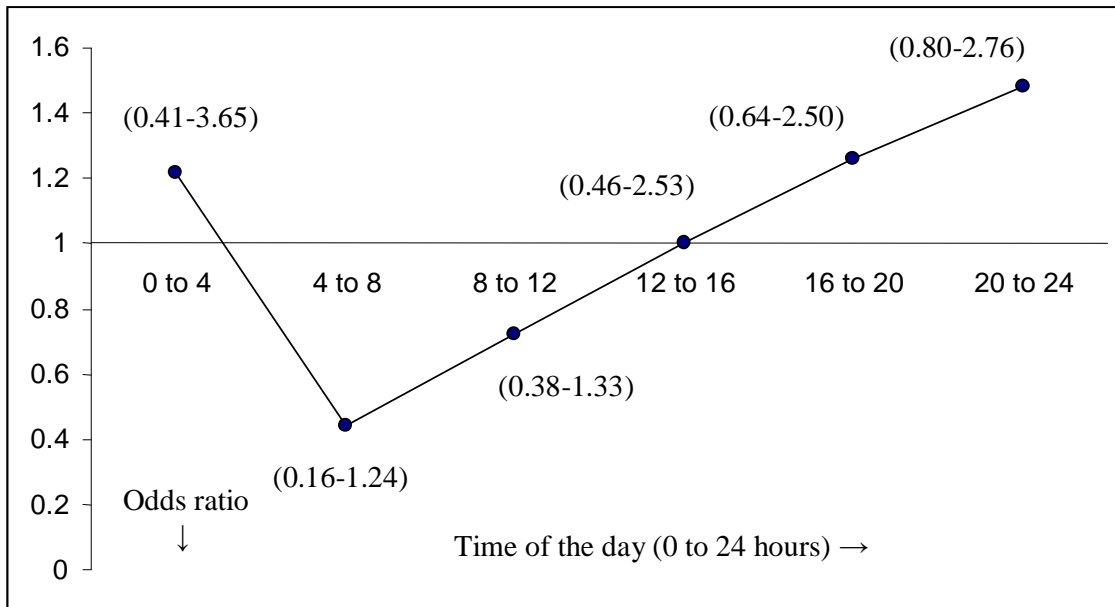


Fig. 1. Odds of having cardiovascular events among those on prophylactic drugs compared to those not on prophylaxes at different times of the day (95.0% CI).