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IMPORTANCE OF NON-DIPPING PATTERN IN CHRONIC KIDNEY DISEASE PATIENTS

K Naga Jyothi* Assistant Professor, Department of Nephrology, Andhra Medical College, Vishakhapatnam, *Corresponding Author

S Manisha Professor, Department of Nephrology, Osmania Medical College, Hyderabad

Kiran mayi Associate Professor, Department of Nephrology, Osmania Medical College, Hyderabad

S Vali Assistant Professor, Department of Nephrology, Osmania Medical College, Hyderabad

ABSTRACT

INTRODUCTION: Hypertension was prevalent in 80 to 90% of patients with chronic kidney disease (CKD), Hypertension was widely known to accelerate the progression of CKD and increase the risk of cardiovascular (CV) events. In essential hypertension, it was observed that 24hr ambulatory BP and a non-dipping profile were closely associated with increased target-organ damage and a worsened CV outcome than clinic BP.

OBJECTIVE: The purpose of this study was to evaluate the relation between non dipping pattern, traditional risk factors such as age, gender, cholesterol, asymptomatic atherosclerosis markers (LVMI, Carotid IMT, ABI) and cardiovascular mortality in CKD patients.

METHODOLOGY: Patients attending hemodialysis unit and the outpatient department of the Osmania General Hospital were formed as the material of study.

RESULTS: According to the Sleep /Awake BP ratio> 0.9 in their ambulatory BP recordings; The percentage of non dipping pattern was observed in 72% and the remaining 28% had dipping phenomenon. The estimated glomerular filtration rate (eGFR) calculated by Modification of diet in renal disease study (MDRD) equation has ranged around 4.8 to 77 ml/mim/1.73m2 and was negatively correlated with sleep/awake BP ratio. The percentage of diabetes was observed to be higher in the non-dippers. The non-dipping phenomenon was significantly associated with asymptomatic atherosclerosis markers (LVMI, Carotid IMT, and ABI). There was a high prevalence of CV events (1 in dipper and 17 in non-dippers) and CV related deaths (1 in dipper and 9 in non-dippers) in non dippers.

KEYWORDS : chronic kidney disease, cardiovascular, non-dipping, LVMI, ABI.

INTRODUCTION:

Cardiovascular disease is a leading cause for morbidity and mortality in chronic kidney disease patients. Cardiovascular risk markers include age, hypertension, carotid intima-media thickness (CIMT), left ventricular mass Index (LVMI) and ankle brachial index (ABI). Ambulatory blood pressure monitoring (ABPM) is a technique of Blood pressure (BP) measurement that may decrease variability of measured BP, It is also an important tool for clarifying the mean level of BP, nocturnal hypertension, and the dipping phenomenon.[1,2] Non-dipping is a blunted nocturnal dip in BP (sleep awake systolic BP ratio >0.9) detected by ambulatory BP monitoring. The prevalence of non-dipping has increased in patients with Chronic Kidney Disease (CKD) and increases with worsening renal function. Abnormal circadian BP variation is a further risk factor leading to accelerated renal decline and atherosclerosis in patients with renal disease.

The purpose of this study was to evaluate the prevalence of non-dipping in CKD patients and evaluate the relation between the abnormal circadian rhythm of BP and the traditional risk factors such as age, gender, cholesterol, asymptomatic atherosclerosis markers (LVMI, Carotid IMT, ABI) and cardiovascular mortality in CKD patients.

METHODOLOGY:

Patients attending hemodialysis unit and the outpatient department of the Osmania General Hospital had been formed as the material of study. A unit of 40 patients who were on hemodialysis (HD) and 31 patients who were in pre-dialysis stage were studied from 2013- 2015. ABPM was performed on HD patients during an Inter-dialysis day after the midweek HD session for 24hrs. Ambulatory BPs were recorded every 30 min during the day (06:00-22:00 hrs) and every 30 min during the night (22:00–06:00 hrs) using Meditech ABPM 05 monitor.

At least 70% of BP recordings during daytime and night-time periods should be satisfactory, or else the monitoring was repeated. BP normally decreases during the night, this is defined as 'dipping'. It is generally agreed that a nocturnal BP fall of 10% of daytime values (night–day BP ratio < 0.9) will be accepted as an arbitrary cutoff to define subjects as 'dippers'. The two dimensional and M-mode echocardiography was performed; Left ventricular mass was determined from M-mode measurements by the method of Devereux and indexed to body surface area (Du Bois Formula). Ultrasonographic scanning of the carotid artery was performed; the measurement of CIMT was done in a plaque-free section in the common carotid arteries.

Ankle-brachial index (ABI) was measured using BP sphygmomanometer. Follow-up duration was calculated from the date of ABPM to the end of study or to the date on which an outcome of death occurred. The entire data has been analysed in Statistical Package for the Social Sciences (SPSS) software. Data was expressed as the mean ± Standard deviation (SD) or as a percentage value. Relationship between estimated glomerular filtration rate (eGFR) and sleep/awake systolic BP ratio was estimated using Pearson's correlation. A two tailed t-test was performed to detect differences among the mean values of the groups, and the chi-square test was used to detect differences among the rates of prevalence of groups such as non-dippers and dippers.

RESULTS:

The results of ABPM, daytime BP, 24hr mean BP and office BP readings were comparable between the dipper and non-dipper groups. The night time BP was higher in nondippers than in dippers. According to Sleep /Awake BP ratio> 0.9 in their ambulatory BP recordings; 51 out of 71 patients (72%) were defined as non-dippers and the remaining 20 patients (28%) as dippers. The demographic variables, serum biochemistry and baseline characteristics of the two groups were shown in the following table 1.

Table 1: Characteristics between Non Dippers and Dippers

	Sleep /Awake BP ratio > 0.9(Non-Dippers)	Sleep /Awake BP ratio < 0.9(Dippers)	P Value
Age (in yrs)	44.76 ± 12.8	44 ± 10.3	.80911
Gender(Male/Female)	**37/14**	**10/10**	
Diabetes	24(47%)	6(30%)	0.19
BMI (kg/m^2)	21.46 ± 3.08	22.255 ±1.90	.283083
Mean GFR (ml /min)	20.44 ± 19.16	31.1 ± 23.35	.05175
Mean S Albumin(g/dl)	3.30 ± 0.49	3.60 ± 0.42	.020697*

Mean S Calcium(mg/dl)	8.84 ± 0.41	8.92 ± 0.40	.49466
Mean S Phosphorus (mg/dl)	3.90 ± 0.46	3.68 ± 0.28	.049843*
Mean LDL – C (mg/dl)	110.10 ± 24.69	114.55 ± 14.47	.227024.
Mean Office SBP mm of Hg	147.45 ± 18.90	146.8 ± 17.30	.894172
Mean Office DBP mm of Hg	86.74 ± 10.68	84.6 ± 11.37	.457446
Mean Office MAP mm of Hg	106.64 ± 11.99	105.15 ± 12.04	.638116
Mean 24 hr SBP mm of Hg	137.66 ± 18.22	133.45 ± 15.85	.367025
Mean 24hr DBP mm of Hg	81.27 ± 8.10	82.15 ±13.30	.736392
Mean 24 hr MAP mm of Hg	99.78 ± 10.50	98.35 ± 14.18	.642288
Mean day SBP mm of Hg	137.86 ± 17.56	138.8 ±15.77	.835915
Mean day DBP mm of Hg	82.37 ± 8.46	85.8 ± 13.10	.196531
Mean night SBP mm of Hg	136.39 ± 19.59	122.8 ± 15.41	.196531
Mean night DBP mm of Hg	78.33 ± 9.84	73.25 ± 14.77	.096025
Mean EF %	58% ± 0.063	60% ± 0.049	.267404
Mean LVMI (g / m^2)	110.08 ± 24.86	97.45 ± 21.52	.049878*
Mean CIMT (mm)	0.82 ± 0.21	0.65 ± 0.14	.00183*
Mean ABI	0.94 ± 0.15	1.06 ± 0.07	.000856*
Mean follow up	19.05 ± 5.53	18.8 ± 4.24	0.425

* - Significant values

The eGFR was calculated by Modification of diet in renal disease study (MDRD) equation has ranged from 4.8 to 77 ml/mim/1.73m^2 and was negatively correlated with sleep/awake BP ratio (r value -0.50, pvalue <0.00001).

The percentage of diabetes was observed to be higher in non-dippers and the P value found to be 0.19 by chi square test indicating a non significant value. The non dippers had higher mean values of LVMI and ICMT and low values of Serum albumin and ABI than dippers which was statistically significant.

Table 2: Association of Non dipping and Markers of Atherosclerosis

	LVMI	ABI	ICMT	eGFR
Non dipping	R : 0.3801	R : -0.4705	R: 0.4573	R: -0.50
	P : 0.001077*	P : 0.000035*	P: 0.000062*	P : <0.00001*

* - Significant values

In the present study it was observed that there was a significant association between nondipping and markers of Atherosclerosis. A positive correlation was observed between LVMI , ICMT and sleep/awake BP ratio and a negative correlation with ABI and eGFR.

Follow up: The mean duration of follow up of the entire cohort was 18.9 ± 5.18 months. During the follow-up period, 18 cardiovascular (CV) events (1 in dipper and 17 in non-dippers) and 10 CV-related deaths (1 in dipper and 9 in non-dippers) and 6 non CV-related deaths (2 in dippers and 4 non-dippers) have occurred.

Table 3: Incidence of adverse events and deaths in Dippers and Non-dippers.

Incidence of Adverse event		
	Dippers(20)	Non dippers(51)
Congestive Heart Failure	1	10
Acute coronary syndrome	0	4
Cerebro vascular accident	0	3
Total adverse events	1(5%)	17 (33.3%)
P value -.030359	Incidence of adverse and non adverse events in dippers and non dippers by chi-square test	

Incidence of Deaths		
	Dippers(20)	Non dippers(51)
Sudden cardiac death	0	3
Myocardial Infarction	0	3
Cerebrovascular accident	0	2
Cardiac failure	1	1
All CV deaths	1	9
Non CV deaths	2	4
Total Deaths	3(15)	13(25.5)

*There are no CV related deaths in the dippers during the follow up period

DISCUSSIONS:

Hypertension is prevalent in 80 to 90% of patients with chronic kidney disease [3]. Hypertension is widely known to accelerate progression of CKD and increase the risk for cardiovascular events [4].Ambulatory blood pressure monitoring (ABPM) is a technique of BP measurement that may decrease variability of measured BP and is an important tool for clarifying the mean level of BP, nocturnal hypertension and the dipping phenomenon[1,2]. Cardiovascular disease is a leading cause of morbidity and mortality in CKD patients [5]. Cardiovascular risk markers include age, hypertension, carotid intima media thickness (IMT), left ventricular mass (LVM) and aortic stiffness – pulse wave velocity. In essential hypertension, it has been shown that 24 hr ambulatory BP and a non-dipping profile are more closely associated with increased target-organ damage and a worsened CV outcome than clinic BP [17]. The purpose of this study was to evaluate the relation between non dipping pattern, traditional risk factors such as age, gender, cholesterol, asymptomatic atherosclerosis markers (LVMI, Carotid IMT, ABI) and cardiovascular mortality in CKD patients.

The prevalence of non-dipping profile in the study was about 72%. Of which 78% were males. This was comparable with other studies like African American study of kidney disease (AASK)[6] study in which the prevalence of non-dippers was 80%, in a study by liu et al[7] the prevalence of non-dippers was 70% and in a study by Mojon et al[8] the prevalence of non-dippers was 61%.

Table 4: Prevalence of non-dipping in CKD population

profile	Number	Prevalence
AASK	617	80%
Liu et al	80	70%
Mojon et al	3227	61%
Study	71	72%

Another observation in the study was that the eGFR measured by MDRD was both negatively and significantly correlated with the non-dipping pattern (r: - 0.50, p <0.00001). The non-dipping status has been noted to be inversely related to kidney function in several studies like Mojon et al.(r: - 0.086, P < 0.014). The percentage of diabetes was observed to be higher in non-dippers (47%) similar to that observed in study done by Liu et al .

Another important observation in our study was that the non-dipping phenomenon was significantly associated with asymptomatic atherosclerosis markers (LVMI, Carotid IMT, and ABI).

Table 5: Studies on correlation between non-dipping and LVMI

Author	Setting	ABPM sessions	Subjects (n)	Association
Cuspidi et al[9].	Never-treated	Two 24-hr sessions within 4 weeks	375	Yes
Rahman et al[10]	Hemodialysis patients	Three 24-hr sessions within 12 months	59	Yes
Heskens etal.[11]	Untreated hypertensives	Two 24-hr sessions within 1 week	150	Yes
Ijri et al.[12]	Untreated hypertensives	Single 48-hr session	56	Yes
Nishikimi et al.[13]	Hemodialysis patients	Single 48-hr session	35	No
Fagugli etal [14]	Hemodialysis patients	Single 48-hr session	66	No

Iida et al.[15]	Middle-aged and elderly hypertensives	Single 48-hr session	255	Yes
Study	CKD patients	Single 24-hr session	71	Yes

Correlation of Ankle Brachial Index (ABI) and CMIT with non-dipping pattern:

In the present study the mean ABI index was significantly lower in non dippers (0.94 $\pm$ 0. 15) than in dippers (1.06 $\pm$ 0.07). ABI was negatively and significantly correlated with non dipping pattern.

The mean CIMT was significantly higher in non dippers and showed significant positive correlation with non dipping pattern. These results were similar to the studies done by Hayam A et al[16].

Association of CV events and deaths with non dipping pattern:

During the follow up period of 18.9 $\pm$ 5.18 months, 18 CV events (1 in dipper and 17 in non-dippers) and 10 CV-related deaths (1 in dipper and 9 in non-dippers) and 6 non CV-related deaths (2 in dippers and 6 non-dippers) have occurred. There was a high prevalence of CV events and deaths in non dippers as observed by Liu et al .

Significance of Non dipper status:

The recent literature does not provide any indisputable association between non-dipping status and sub-clinical cardiac organ damage. Several methodological problems may explain these conflicting findings.

It is generally considered that 10% threshold value separates dippers from non-dippers as an arbitrary value. A second critical issue concerns the definition of night-time and daytime periods. The third issue is that it has a limited reproducibility over time as night-time BP is influenced by the quality of sleep, and this is not commonly monitored in ABPM studies. Significant variability in the classification of subjects as dippers and non-dippers by repeating the recordings twice after several months has been reported previously. However, the problem of obtaining a reliable and reproducible characterization of dipping status in the individual patient could not be satisfactorily solved yet because of interference by several other confounders, such as age, diabetes mellitus, smoking habits and degree of working activity during the daytime hours, and body position during the nighttime hours.

CONCLUSIONS:

Finally, we cannot set a cause effect relationship based on this associative and limited study. Good quality, long term, large longitudinal trials are required to validate the role of non-dipping BP pattern in clinical practice for patients with CKD.

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