

Assessment of dipping status of systemic blood pressure by 24 hour Ambulatory Blood Pressure Monitoring (ABPM) in patients with features of optic nerve head (disc) changes of Optic Neuropathy

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ABSTRACT

Background: Optic neuropathy is a spectrum of disease of different etiology, and especially when associated with systemic disease like hypertension, where there is effect on auto regulation mechanism of the ocular perfusion.

Aim: To see the blood pressure behavior and dipping status by 24 hour Ambulatory Blood Pressure Monitoring among patients who were diagnosed to have features of secondary optic neuropathy whether they were hypertensive or not.

Methods: Ninety-four patients were included in a cross sectional study, and using specific exclusion criteria, 38 patients were having changes of optic neuropathy as diagnosed by optical coherence tomography, with 56 other patients as a control group. All were examined and investigated, and subjected to 24 hour Ambulatory Blood Pressure Monitoring test using specific device (CONTEC™ - AUTOMATIC BP MONITOR - MODEL: ABPM50) and the data from the device were displayed to the computer for measurement and analysis. The dipping status was calculated manually using a specific formula. The data, then fed to SPSS software version 20 for statistical analysis.

Results: There was no statistical significance for age, sex, BMI and other risk factors like hypertension, diabetes mellitus and dyslipidemia. Reverse or blunted response was common among hypertensive patients in both studied groups, but the P-value not significant.

Conclusion: This study showed that there was no specific BP dipping pattern by ABPM in the studied patients with optic neuropathy in our locality.

Key words: Optic neuropathy, Ambulatory Blood Pressure Monitoring, Dipping state.

Abbreviations:

ABPM = Ambulatory Blood Pressure Monitoring; ONP = Optic Neuropathy; BMI = Body Mass Index; OPP = Ocular Perfusion Pressure; IOP = Intra Ocular Pressure; OCT= Optical Coherence Tomography; FDEMC = Faiha Specialized Diabetes Endocrine and Metabolism Center ESH = European Society of Hypertension; DM=Diabetes Mellitus; AHA = American Heart Association.

تقييم حالة الانخفاض لضغط الدم الجهازي بواسطة مراقب الضغط المتنقل ٢٤ ساعة عند المرضى الذين لديهم علامات اعتلال العصب البصري

الخلفية: اعتلال العصب البصري هو طيف من الامراض مختلفة الاسباب، خصوصا عندما تكون مصاحبة للأمراض الشاملة مثل ارتفاع ضغط الدم، حيث ان هناك تأثير على ميكانيكية التنظيم الالي للتروية البصرية.

الهدف: رؤية تصرف ضغط الدم والحالة الأنخفاضية بواسطة مراقب الضغط المتنقل ٢٤ ساعة عند المرضى الذين لديهم علامات اعتلال العصب البصري بغض النظر عن اصابتهم بارتفاع ضغط الدم من عدمه.

الطرائق: شملت الدراسة ٩٤ مريضا في دراسة مقطعية باستخدام معايير استثنائية خاصة، ٣٨ مريضا كانت لديهم تغيرات اعتلال العصب البصري مشخصة بفحص التماسك البصري المقطعي، و ٥٦ مريضا مجموعة قياسية. جميع المرضى تم فحصهم سريريا ومختبريا، واجري

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لهم فحص مراقبة الضغط ٢٤ ساعة المتنقل باستخدام جهاز خاص (CONTEC™ – AUTOMATIC BP MONITER–MODEL:ABPM50) واخذت المعلومات وعرضت في الحاسوب للقياس والتحليل. تم احتساب حالة الانخفاض يدويا وفقا لمعادلة خاصة. تم تغذية المعلومات الى برنامج SPSS النسخة ٢٠ للتحليل الاحصائي. النتائج: لم يكن هناك اهمية احصائية للعوامل: العمر، الجنس، معامل كتلة الجسم، وبقية عوامل الخطورة مثل ارتفاع ضغط الدم، مرض السكري، واضطراب الدهون. الاستجابة العكسية او المخشنة كانت السائدة عند مرضى ارتفاع ضغط الدم في كلا المجموعتين لكن القيمة الاحتمالية لم تكن مهمة. الاستنتاج: هذه الدراسة اوضحت انه لا يوجد نموذج خاص للحالة الانخفاضية باستخدام مراقب الضغط المتنقل ٢٤ ساعة عند المرضى الذين تمت دراستهم في هذه العينة المصابين باعتلال العصب البصري. الكلمات المفتاحية: اعتلال العصب البصري. مراقب الضغط المتنقل ٢٤ ساعة. الحالة الانخفاضية.

INTRODUCTION

Reduction of the ocular perfusion pressure and disturbed vascular auto-regulation are the cornerstones of the vascular hypothesis that leads to optic nerve damage. Physiological changes in circadian rhythm may further aggravate ischemia of optic nerve mainly by fluctuation in ocular perfusion pressure (OPP), which is derived from intraocular pressure (IOP) and mean arterial pressure. Many researchers have drawn attention that both the physiological reduction in systemic BP during sleep, and excessive hypotensive effect of antihypertensive drugs used in the treatment of hypertension, may lead to a secondary reduction of perfusion in the vessels of the eye and the orbit, chronic ischemia and neuropathy of the optic nerve.^[1-3] The diagnosis of optic neuropathy need detailed history and neuro-ophthalmological examination assisted by laboratory studies and imaging, where the optical coherence tomography (OCT) is the method of choice done by the ophthalmologist because it can detect the early features by documentation of peripapillary nerve fiber thickening in subtle cases.^[4] Systemic hypertension, arteriosclerosis, vasospasm, or medication may reduce the auto-regulation capacity of the optic disc. Exaggerated nocturnal hypotension may be seen in patients with aggressive antihypertensive therapy,

especially if taken a right before bedtime.^[5] Ambulatory Blood Pressure Monitoring (ABPM) is the best method for assessing BP during day time and sleep and give an idea about the morning surge and night dipping, where both of these parameters have important prognostic implications.^[6,7,8] There is a compelling evidence that nocturnal BP is superior to daytime pressure in predicting outcome.^[9-11] Most ABPM devices available have been validated independently according to the internationally accepted validation protocols, the most popular of which is the International Protocol of the European Society of Hypertension (ESH).^[12] Dipping status assessment depends on the behavior of BP from wakefulness and sleep, depending on whether BP falls, rises, or remain constant. The indication of ABPM underwent revolution and progress in the different group of hypertensive patients for follow-up and / or to establish the diagnosis of hypertension,^[13] and also as a prognostic indicator of the cardiovascular, cerebrovascular, renal, and ophthalmological outcome. And many studies were done utilizing ABPM for evaluation of patients with optic neuropathy especially hypertensive on treatment, or those with the hypotension of different etiology.^[14-16] *The aim of the study*, you study BP behavior of and the state dipping by 24 ABPM among

patients who were diagnosed to have features of optic disc neuropathy whether they were hypertensive or not, and also to study other factors that might have a role or associated as a cause for optic neuropathy, in comparison with the control group of patients.

Methodology, this is a case-control study involving 94 patients, that were seen in collaboration between physicians and one ophthalmologist. Thirty-eight (38) patients of them have features of optic neuropathy, who fulfill the definition of optic neuropathy in its early states and that is related to the defect in the ocular blood perfusion-and may lead to ischemic optic neuropathy, that were diagnosed by OCT and other tools including IOP measurement and visual field assessment, regardless their state of hypertension or the treatment. Their complains were different with no specific signs, symptoms or presentation, or were referred to him to exclude ophthalmological problem. With 56 patients with similar demographic characteristics, and have no features optic neuropathy, were taken as a control group for comparison. The study done in Faiha Teaching Hospital in Basrah Southern of Iraq between Feb 2016 to June 2017. Exclusion criteria; patients with glaucoma and obvious increased IOP and other causes or types of optic neuropathy apart from ischemic type (look for the appendix 1 of the causes), like arteritis optic neuropathy, or patients on medication that are known to cause optic neuropathy other than antihypertensive including topical eye preparations (*B*-blocker) or drug used for erectile dysfunction, previous stroke, previous history of eye surgery or laser therapy, having autonomic dysfunction of different causes, patients with SOL or malignancy or on treatment for malignant disease, patients with irregular arrhythmia or heart failure, chronic kidney disease. All patients were studied their basic information including; age, sex, BMI, history of

hypertension, diabetes mellitus dyslipidemia and the type of different types and time of medication(s) and the demographic data and were subjected to laboratory investigation and 24ABPM using a specific device (**CONTEC™ - AUTOMATIC BP MONITOR – MODEL: ABPM50**) then we upload patient's data to the computer, and allowed the patient for 24 hours to practice their daily activity or job and later we download the results, and most of the data were analyzed by device presetting, and some of the parameters or data used in study were analyzed manually. Ten patients their data were excluded and not enrolled in the study because of the technical errors. Sections of the device readings were portioned to include; the time and the average arterial BP in systole and diastole, BP load in day and night, maximum and minimum systolic and diastolic BP, pulse rate and mean arterial BP, and circadian rhythm. The definition of hypertension, diabetes mellitus, dyslipidemia and BMI was according to their last accepted international definition. Classification of dipping was according to AHA by the formula; {Dip = (1- SBP sleeping/SBP waking) x100 = -- %}.^[17] We may have four classes of dipping: ≤ 0% = reverse dipper, 0% - 10% = nondipper, 10-20% = normal dipper, extreme dipper ≥ 20%. Or by the formula that was used by the device of the ABPM in this study, {Dipping = averages BP sleeping \average SBP day time},^[18] and we may have four classes of dipping, ≤ 0.8=severe or extreme dipper, ≥ 0.8 - ≤ 0.9 = normal dipper, ≥ 0.9 - ≤ 1.0 blunted or non-dipper, ≥ 1.0 Reverse dipper. These are corresponding to the classes in AHA formula.

Statistical analysis: Data were collected and fed to SPSS software version 20 for statistical analysis. Continuous data were compared using Student's t - test, while categorical data were analyzed by cross-tabulation and obtaining Odd's ratio and P-

value and Chi-squared test. The P value less than 0.05 considered an indication of a significant statistical inference.

RESULTS

The basic characteristics of the sample and potential risk factors distribution

As seen in (table-1), the age and sex distribution were matched but there was no

significant statistical difference between cases and control. This was also applied for BMI which was not different in both groups. The distribution of hypertension, diabetes and hyperlipidemia were similar that there was no significant statistical association. It was statically difficult to assess the use of antihypertensive medication and the timing of the doses, so they were not mentioned.

Table 1. Baseline characteristics of the patients

		Cases	Control	P Value
Age (mean ± SD)		51.24 ± 10.70	47.87 ± 15.30	0.249
Sex	<i>Male</i>	14 36.84%	27 50%	0.235
	<i>Female</i>	24 63.15%	27 50%	
BMI	<i>Male</i>	27.46 ± 3.92	28.95 ± 6.00	0.424
	<i>Female</i>	29.18 ± 5.38	28.94 ± 4.24	0.861
Hypertension		24 63.15%	39 72.22%	0.575
Diabetes		13 34.21%	11 20.37%	0.194
Hyperlipidemia		17 44.73%	23 42.59%	0.947

The device measurements and the relation to optic nerve head disease.

Directly reported measurements of the 24 hours BP monitoring were studied using Student’s t-test to detect possible differences between cases and control individuals. (Table-2), shows the direct measurements comparison where it was not possible to detect a significant statistical difference between the two groups. (Table-2), displays selected parameters only because of a large

number of parameters which carry the same inference of absence of significant difference between cases and control groups regarding device measurements. Hence, parameters like day BP, night BP, maximum systolic, minimum systolic, maximum diastolic and minimum diastolic BP not displayed in (Table-2).

Table 2. direct device parameters in 24 ABPM examinations

Parameters (mean ± SD)	Cases	Control	P value
All systolic BP	123.74± 17.28	122.38± 16.38	0.700
All diastolic BP	72.06 ±11.44	71.90±9.74	0.943
Day BP load (more than 140 mmHg)	31.49 ± 29.08	23.44± 12.37	0.445
Day diastolic load (more than 90 mmHg)	17.83± 12.79	16.21± 7.67	0.702
Night BP load	45.90 ± 9.31	36.14± 7.72	0.233
Day BP load	21.4±3.96	19.92± 7.91	0/817
Systolic night des	5.87 ± 3.18	8.10 ± 3.15	0.535
Diastolic night des	6.38 ± 1.29	10.31 ± 6.09	0.336
Mean pulse pressure/ Day	54.49 ± 10.08	52.78 ± 11.28	0.452
Mean pulse pressure/ night	50.39 ± 8.97	48.70 ± 9.82	0.398
Mean arterial BP/ day	91.90 ± 12.12	90.43 ± 11.44	0.556
Mean arterial BP/ Day	83.88 ± 13.23	79.85 ± 12.59	0.144

The analysis of dipping states.

BP dipping studied by different methods, however in both approaches there was no significant difference in cases and control groups. (Table-3), shows the statistics of both methods of dipping assessment. The relation

between the two classifications was further investigated by Pearson Correlation Coefficient, and revealed an inverse strong relationship with an r of 0.837 and a P-value of less than 0.001.

Table 3. Correlation between the methods of assessment of dipping status

Parameters	Cases	Control	P value
BP dipping percentages (mean \pm SD)	0.930 \pm 0.178	0.913 \pm 0.131	0.549
BP dipping percentages in AHA (mean \pm SD)	6.72 \pm 1.79	7.25 \pm 1.68	0.895
Pearson's Correlation Coefficient	0.837		Less than 0.001

Categorical classification of BP dipping into severe, normal, blunted and reverse revealed that there is a significant agreement between

the two classifications with Kappa value of 0.578 as shown in (Table-4).

Table 4. Level of agreement between the classification approaches of dipping status

Classification Design of dipping state		Aha classification				Total
		Less than 0% (reverse)	0-10% (blunted)	10-20% (dipper)	More than 20% (severe)	
Dipping category	Severe	0	0	0	12	12
		0.0%	0.0%	0.0%	100.0%	12.8%
	Normal	0	0	28	0	28
		0.0%	0.0%	96.6%	0.0%	29.8%
	Blunted	0	31	1	0	32
		0.0%	96.9%	3.4%	0.0%	34.0%
	Reverse	21	1	0	0	22
		100.0%	3.1%	0.0%	0.0%	23.4%
Total		21	32	29	12	94
		100.0%	100.0%	100.0%	100.0%	100.0%

Comparison of both methods of dipping was identical in cases and control individuals

according to statistical test and the corresponding P-value as seen in (Table-5).

Table 5. Correlation of the dipping state according to the methods of dipping assessment

		Type		Total	P value for Dipping	P value for dipping in aha classification
		Case	Control			
Dipping category	Severe	5	7	12	0.937	0.793
	Normal	10	18	28		
	Blunted	14	18	32		
	Reverse	9	13	22		
Total		38	56	94		

In (Table-6), the percentage of patients in dipping was approximate, yet there was no both groups and different categories of statistical significance.

Table 6. Relation of optic neuropathy and state of dipping according to the hypertension state.

Dipping Category	Cases			Control		
	Hypertension		Total	Hypertension		Total
	No	Yes		No	Yes	
Severe	1	4	5	4	3	7
	7.1%	16.7%	13.2%	25.0%	7.7%	12.7%
Normal	4	6	10	6	12	18
	28.6%	25.0%	26.3%	37.5%	30.8%	32.7%
Blunted	5	9	14	4	14	18
	35.7%	37.5%	36.8%	25.0%	35.9%	32.7%
Reverse	4	5	9	2	10	12
	28.6%	20.8%	23.7%	12.5%	25.6%	21.8%
Total	14	24	38	16	39	55
	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

P value = 0.247

DISCUSSION

In this study, the age in both groups was approximately matched, and the control group was an equal number for both sexes while in the case group there is female predominance. BMI in both groups was approximate. Age, sex, and BMI all constitute no statistical significance; findings that are consistent with the results of different studies that found that optic neuropathy can affect patients at any age, and 10% being under 45, and both male and female are equally affected.^[19] Although more than 2\3 of the patients in both groups were hypertensive, and more than 40% had dyslipidemia, but this constitutes no statistical significance. The same applies to DM, though the number among case group (13) 34.2% versus (11) 20.3% in control group. The results of the previously mentioned factors were different to the results of many studies that show systemic disease associations for hypertension, and DM only for patients with optic neuropathy who were between 45-64 years of age, and in

another study, there was a strong association with obstructive sleep apnea.^[20,21,22] The later may also be related to the increase in the BMI, and the explained hypothesis that apneic spells might result in an acute increase in BP, intracranial pressure, and nocturnal hypoxia that could cause optic neuropathy.^[23] One study shows that hypercholesterolemia associated with optic neuropathy in younger patients. And optic neuropathy may be the first manifestation of a lipid disorder.^[24] Although it was difficult to analyze the specific antihypertensive drugs and their timing of administration statistically, yet many studies show that many systemic drugs have ocular and visual side effects, and specifically nonselective B-blocker decrease IOP, and topical B-blocker also produce little additional IOP reduction.^[25,26] Beata Krasinska, and colleagues, showed that taking anti-hypertensive drugs in the evening may significantly decrease blood flow in the eye arteries, cause degenerative changes within the optic nerves.^[27] The device parameters

for ABPM shown in (Table-2), also show no significant statistical value, and this may be due to the fact that the optimal information obtained from ABPM and their interpretation still in progress and discussion, regarding the duration and timing of day and night, the frequency of measurements, and BP variability effect on interpretation of the results.^[28] One similar case- control study showed that relative hypotension was due to over treatment of hypertension or due to abnormal vascular auto regulation, that results in a low mean BP and a lag in the usual rise of the BP in the morning.^[29, 30] In this study, the reverse and blunted pattern of dipping were the commonest pattern in hypertensive patients in both groups, followed by normal dipping pattern, and the least was severe dipping. But the effect of treatment of antihypertensive treatment on dipping was not studied because of the statistical difficulties of sample size. These findings are consistent with a study from Spain and other cohorts studies from Europe, USA, and Asia, that conclude that a blunted pattern of dipping is common in hypertensive patients, and in the treated patients the blunted pattern was associated with the use of higher number of antihypertensive drugs but not with the time of taking the medication.^[31,32] However many studies relate the nocturnal dipping in BP as the basic mechanism for the optic nerve head changes and ocular ischemic disorders like anterior ischemic optic neuropathy, normal tension glaucoma ,primary angle glaucoma, and other optic nerve head disorders.^[33] Systemic diseases, local, physiological and anatomical factors also play role in the mechanism optic nerve head derangement.^[34] The ABPM as method for assessment of dipping state is also a matter of investigations and frequent changes in the recommendations especially in hypertensive and diabetic patients, where single test usually is not enough for classification of the

dipping state, assessment of treatment type and timing, that strengthen, change or sometimes argue against the recommendations, like the American Diabetic Association(ADA) reported to use more than one antihypertensive drugs at bedtime,^[35] which is now changed so that the aim of treatment is to reduce nocturnal hypertension, and clinical studies suggest to have more collaboration and arrangement between ophthalmologists and physicians while dealing with hypertensive patients who have sight- threatening clinically and supported by OCT examination which can detect retinal nerve fiber layer involvement specific to different class of visual field defects in eyes with non-arteritic optic neuropathy.^[36] Although the ABPM since it was introduced in the medical practice before 1978 and in spit of frequent meetings and reviewing the optimization of the test and the indications by many researches and literatures and now strongly become part of daily medical practice and has its own committees and guidelines on the other hand there are still controversies rise frequently like the threshold of the BP, the frequency and the number of the tests that are needed, the indications and limitations of the test, and device and software pitfalls in interpreting the results.^[37] yet in our society is underused and there is no good awareness among the physicians.

In conclusion, this study shows that there was no specific BP dipping pattern by ABPM in this sample of the studied patients with optic neuropathy, and the development of the changes for optic neuropathy is multifactorial, and none of the risk factors that were studied can be regarded as an independent cause for optic neuropathy.

Limitations

The main limitations to this study; the sample size was limited and difficult to repeat the ABPM test, and to follow and repeat the ophthalmologic examination by OCT.

Recommendation

More cooperation and awareness between physicians and ophthalmologists is needed while dealing with patients with systemic diseases, and scheduled examination for early detection of sight-threatening diseases. And to institute local foundation for optic nerve disease.

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