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นิพนธ์ต้นฉบับ

ความชุกและปัจจัยที่สัมพันธ์ต่อการเกิดภาวะระบบประสาทอัตโนวัติทำงานผิดปกติ ในผู้ป่วยโรคไตเรื้อรังที่ได้รับการบำบัดทดแทนไต ด้วยวิธีการล้างไตทางช่องท้องแบบต่อเนื่อง

ณัฐธยา วชิรพันธุ์สกุล พ.บ., กัญญณัท บุณยทรรพ พ.บ.,
ธนวัฒน์ วงศ์ชัยอุดมโชค พ.บ.
กลุ่มงานอายุรกรรม โรงพยาบาลลำปาง

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คำสำคัญ:
ระบบประสาทอัตโนวัติทำงานผิดปกติ,
ล้างไตทางช่องท้องแบบต่อเนื่อง,
เบาหวาน,
ภาวะน้ำหนักเกิน

บทคัดย่อ

ภูมิหลัง: ระบบประสาทอัตโนวัติทำงานผิดปกติ (autonomic dysfunction, AD) พบได้บ่อยในผู้ป่วยโรคไตเรื้อรัง (CKD) อาจทำให้เกิดความดันโลหิตต่ำ หัวใจเต้นผิดจังหวะ และการเสียชีวิตเฉียบพลัน ยังขาดข้อมูลของภาวะนี้ในผู้ป่วย CKD ที่ได้รับการบำบัดทดแทนไตด้วยวิธีการล้างไตทางช่องท้องแบบต่อเนื่อง (CAPD)

วัตถุประสงค์: เพื่อศึกษาความชุกและปัจจัยที่สัมพันธ์กับภาวะ AD ในผู้ป่วย CKD ที่ได้รับ CAPD

วัสดุและวิธีการ: เป็นการศึกษาเชิงสังเกตการณ์แบบไปข้างหน้า ในผู้ป่วย CKD ที่ได้รับ CAPD ในศูนย์โรคไต รพ.ลำปาง ช่วงเดือน ส.ค.2562 - ม.ค.2563 ทดสอบภาวะ AD ด้วยการตรวจคลื่นไฟฟ้าหัวใจเพื่อประเมินการตอบสนองของอัตราการเต้นของหัวใจต่อการหายใจลึกใน 1 นาที วิเคราะห์ทางสถิติเปรียบเทียบระหว่างกลุ่มที่มีและไม่มีภาวะ AD วิเคราะห์หาปัจจัยที่สัมพันธ์กับการเกิดภาวะ AD ด้วย regression analysis

ผลการศึกษา: ผู้ป่วยเข้าร่วมในการศึกษา 130 ราย พบว่ามีภาวะ AD 93 ราย (ร้อยละ 71.5) พบโรคเบาหวานและภาวะน้ำหนักเกิน ในกลุ่ม AD มากกว่ากลุ่ม non-AD (ร้อยละ 51.6 *vs* 27.0, p=0.012 และร้อยละ 49.5 *vs* 21.6, p=0.005, ตามลำดับ) อัตราส่วนของผู้ป่วยในกลุ่ม AD ที่ได้รับยาขับปัสสาวะ (ร้อยละ77.4 *vs* 56.8, p=0.030) และ beta-blocker (ร้อยละ 60.2 *vs* 32.4, p=0.006) มีสูงกว่ากลุ่ม non-AD ปัจจัยที่สัมพันธ์กับการเกิดภาวะ AD เมื่อวิเคราะห์ด้วย univariate analysis คือ ภาวะน้ำหนักเกิน (OR 3.55, 95%CI 1.47-8.57, p=0.005), โรคเบาหวาน (OR 2.88, 95%CI 1.25-6.62, p=0.013), การได้รับยา beta blockers (OR 3.15, 95%CI 1.41-7.05, p=0.005), ยาขับปัสสาวะ (OR 2.61, 95%CI 1.16-5.88, p=0.02) และเมื่อวิเคราะห์ด้วย multivariate analysis คือ ภาวะน้ำหนักเกิน (OR 2.65, 95%CI 1.03-6.85, p=0.044) และโรคเบาหวาน (OR 2.42, 95%CI 1.01-5.84, p=0.049).

สรุป: ผู้ป่วย CKD ที่ได้รับ CAPD พบความชุกของภาวะ AD ร้อยละ 71.5 ภาวะน้ำหนักเกินและโรคเบาหวานเป็นปัจจัยที่สัมพันธ์กับการเกิดภาวะนี้

ลำปางเวชสาร
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ORIGINAL ARTICLE

Prevalence and Factors associated with Autonomic Dysfunction in Continuous Ambulatory Peritoneal Dialysis Patients

Nuttaya Wachiraphansakul M.D., Kanyanutt Boonyatarp M.D.,

Thanawat Vongchaiudomchoke M.D.

Department of Internal Medicine, Lampang Hospital, Lampang, Thailand

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Corresponding author:
Thanawat Vongchaiudomchoke M.D.,
Department of Internal Medicine,
Lampang Hospital,
280 Phaholyothin Road,
Hua Wiang Subdistrict,
Mueang District,
Lampang 52000, Thailand
Tel. +66 54-237400 ext 8754,
Email: idrwern@gmail.com

Abstract

Background: Chronic kidney disease patients are at risk for autonomic dysfunction (AD). Prevalence and associated factors of AD in patients with continuous ambulatory peritoneal dialysis (CAPD) are not clearly known.

Objective: To determine the prevalence and identify the associated factors of AD in CAPD patients.

Material and method: A prospective observational study was conducted among CKD patients who received CAPD at the Renal Unit, Lampang Hospital from August 2019 to January 2020. Testing for AD by observing an EKG record of heart rate variability during deep breathing (HRVDB) in 1 minute was carried out. The comparison between the AD group and non-AD group was obtained by statistical analysis. The regression analysis was used to determine the associated factors of AD.

Results: A total of 130 CAPD patients were eligible and AD was found in 93 cases (71.5%). Diabetes and overweight were more commonly found in the AD group than the non-AD group (51.6% *vs* 27.0%, p=0.012 and 49.5% *vs* 21.6%, p=0.005, respectively). The AD group received diuretics (77.4% *vs* 56.8%, p=0.030) and beta-blockers (60.2% *vs* 32.4%, p=0.006) more than the non-AD group.The associated factors of AD by univariate analysis were overweight (OR 3.55, 95%CI 1.47-8.57, p=0.005), diabetes (OR 2.88, 95%CI 1.25-6.62, p=0.013), receiving beta blockers (OR 3.15, 95%CI 1.41-7.05, p=0.005) and receiving diuretics (OR 2.61, 95%CI 1.16-5.88, p=0.020). With the multivariate analysis, the associated factors of AD were overweight (OR 2.65, 95%CI 1.03-6.85, p=0.044) and diabetes (OR 2.42, 95%CI 1.01-5.84, p=0.049).

Conclusions: Prevalence of AD in CAPD patients was 71.5%. Overweight and diabetes were significant associated factors.

Introduction

Autonomic dysfunction (AD) is a common neurological complication in chronic kidney disease (CKD) patients. Its prevalence of 50-60% in patients with CKD and hemodialysis has been reported [1, 2] and might contribute to orthostatic hypotension, arrhythmia and sudden cardiac death [3, 4]. Falls of systolic blood pressure >20 mmHg or diastolic blood pressure >10 mmHg within 3 minutes of standing can lead to an adverse event[5]. The risk factors of AD are diabetes, hypertension, obesity and hyperparathyroidism[6-10]. The potential mechanism of AD in CKD is an inhibition of endothelial function and nitric oxide synthase production by uremic toxin, leading to renin-angiotensin-aldosterone system activation. Moreover, protein loss during peritoneal dialysis stimulates albumin and cholesterol synthesis by the liver. The increment of low-density lipoprotein can cause atherosclerosis and increase arterial stiffness which also activates the renin-angiotensin-aldosterone system. These result in decreased baroreflex activity, increased sympathetic as well as decreased parasympathetic nervous system activity, and AD finally[3,11,12].

AD could be diagnosed by several tests including the tilt-table test and the power spectral analysis, but they were cumbersome and not practically available. One-minute heart rate variability during deep breathing (HRVDB) is a simple, non-invasive bedside test with 86% sensitivity and 80% specificity for diagnosis of AD[13]. Moreover, an impairment of heart rate variability was associated with poor clinical outcomes in peritoneal dialysis patients[14].

Neurologic orthostatic hypotension secondary to AD is also a common complication in continuous ambulatory peritoneal dialysis (CAPD). The autonomic function in CAPD patients has been assessed in few studies. AD was presented in uremic patients who were treated with hemodialysis and CAPD. No differences were found between both groups of dialysis[15,16]. Yung et al. illustrated that the prevalence of AD in non-diabetic CAPD patients was 58.4% as measured by sympathetic skin response. The significant associated factors were elderly, malnutrition, low residual renal function and low daily dialysis dose[17]. Nevertheless, the prevalence and associated factors of AD among the diabetic CAPD patients has not been defined. The identification of modifiable etiology could help the physician to prevent this condition and alleviate its adverse outcome. The primary objective of this study aimed to determine the prevalence of AD in both diabetic and non-diabetic CAPD patients. The secondary objective was to identify associated factors of AD in these patients.

Material and methods

A prospective observational study was conducted among CKD patients who received CAPD at the Renal Unit of Lampang Hospital, a tertiary care hospital in northern Thailand, from August 2019 to January 2020. All patients had had dialysis vintage at least twelve weeks before enrolled into the study. They were prescribed standard dose and standard volume CAPD with 1.5% dextrose dialysate fluid, 2 liters/cycle, dwelled time at least 4-6 hours each cycle and exchanged 4 cycles a day. The exclusion criteria were heart failure; arrhythmia (premature ventricular contraction; premature atrial contraction; atrial fibrillation; junctional arrhythmia; atrioventricular block); myocardial infarction; active malignancy; sepsis; peritoneal dialysis-related peritonitis; epilepsy and movement disorder. The research protocol was approved by the institutional review board and registered in the Thai Clinical Trial Study (TCTR ID: 20200111002). Informed consents were obtained from all patients.

Baseline demographic data included age, sex, body mass index (BMI), underlying diseases, dialysis vintage, hemodynamic parameters and current medications. Basic laboratory tests were obtained from the most update data prior to the HRVDB test. The AD was diagnosed by the HRVDB method[18] using an EKG record (ZOLL® R-series monitor/defibrillator, Asahi Kasei, Japan) which recorded during forced deep breathing 6 breaths/minute (5 seconds in and 5 seconds out) in the supine position. It was carried out for 1 minute in a silent room of the renal unit at 25°C room temperature in the morning. Prior recording, the patient was asked to give a forced deep breathing for 6 breaths without EKG record to simulate the real test. Then, the HRVDB was done in a single straight one minute by the medical internist. This procedure was done once for each patient and heart rate variability was calculated. If the abnormal rhythms were detected, those EKG strips were discarded and the test was repeated. If the abnormal rhythms persisted >3 tests, the patient was excluded from the study. The maximum and minimum R-R intervals during each breathing cycles obtained from a single complete EKG strips were measured and converted to beats per minute (bpm). The results were expressed as the mean of the difference between maximum and minimum heart rates, which an abnormal response was ≤ 10 bpm and considered as AD (Fig. 1). The results were interpreted by two independent medical internist and nephrologist. If disagreement occurred, the final result was decided by a nephrologist.

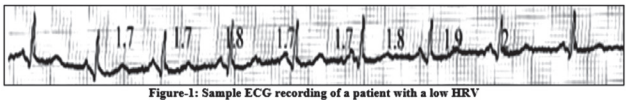

Figure-1: Sample ECG recording of a patient with a low HRV

Fig.1. The maximum and minimum R-R intervals were 2.0 and 1.7 cm respectively, which converted to be 0.8 and 0.68 second between each heartbeat respectively. The maximum and minimum heart rate were 60÷0.8 = 75 and 60÷0.68 = 88 bpm, respectively. Thus, the heart rate variation between the maximum and minimum was 88-75 = 13 bpm.

The sample sizes were calculated from the one proportion formula as following.

$$N = \frac{(Z\alpha/2)^2(p)\ (1 - p)}{d^2}$$

From a pilot study in our renal unit, we found that the prevalence of AD in CAPD patients was about 62% (p=0.62). We assumed the 10% absolute precision (d=0.1) with 95% confidence (α=0.05) and $Z_{\alpha/2}$ = 1.96, then the estimated sample size was 91 patients.

The data were analyzed by using descriptive statistics. Continuous variables were illustrated in mean and standard deviation (SD) for normal distribution and median and interquartile range (IQR) in skewed distribution. Categorical variables were illustrated in number and percentage. The patients were categorized into those with AD (AD group) and without AD (non-AD group). The comparison between the two groups was obtained by using student t-test for continuous variables. For categorical variables, exact probability test and Mann-Whitney U test were utilized. We used regression analysis to determine the associated factors of AD. In univariate analysis, potential factors with p <0.25 or clinically important were included. Interested factors from univariate analysis were then analyzed in multivariate analysis. Statistical analysis was performed by STATA 15.0 (STATA Corp., Texas, USA). A p-value of <0.05 was considered statistically different.

Results

There were 130 patients enrolled in this study and AD occurred in 93 cases (71.5%). Diabetes and overweight were more commonly found in the AD group than the non-AD group (51.6% *vs* 27.0%, p=0.012 and 49.5% *vs* 21.6%, p=0.005, respectively). Patients in the AD group received diuretics (77.4% *vs* 56.8%, p=0.030) and beta-blockers (60.2% *vs* 32.4%,

p=0.006) more than those in the non-AD group significantly, as well as having higher serum potassium (3.9 [SD 0.6] *vs* 3.7 [SD 0.6] mmol/L, p=0.020). There were insignificant differences between the two groups regarding to age, gender, BMI and blood pressure (Table 1-2).

During the HRVDB test, the average of the maximal heart rate in AD group was significantly lower than non-AD group (76.9 [SD 14.5] *vs* 87.7 [SD 11.8] bpm, p<0.001), but that of the minimal heart rate was not different (70.9 [SD 13.9] *vs* 71.9 [SD12.0] bpm, p=0.690). Likewise, the median of the heart rate variability was significantly lower in AD group (6.2 [IQR 4.0-7.5] *vs* 12.7 [IQR 11.6-17.3] bpm, p<0.001).

The associated factors of AD by univariate analysis were overweight (OR 3.55, 95%CI 1.47-8.57, p=0.005); diabetes (OR 2.88, 95%CI 1.25-6.62, p=0.013); receiving beta blockers (OR 3.15, 95%CI 1.41-7.05, p=0.005) and receiving diuretics (OR 2.61, 95%CI 1.16-5.88, p=0.02). The associated factors of AD by multivariate analysis were overweight (OR 2.65, 95%CI 1.03-6.85, p=0.044) and diabetes (OR 2.42, 95%CI 1.01-5.84, p=0.049) (Table 3).

Discussion

Autonomic dysfunction is an important condition which has the capacity to lead to cardiac abnormality, arrhythmia and sudden death. Our study aimed to determine the prevalence and identify associated factors of AD in both diabetic and non-diabetic CAPD patients. The prevalence of AD in our study was 71.5%, higher than previous reports in non-dialytic CKD and hemodialysis patients[1,2]. The higher prevalence in CAPD patients might be contributed by the high prevalence of dyslipidemia from the protein loss during peritoneal dialysis which stimulate hepatic production of albumin and cholesterol-enriched lipoprotein[3]. Nonetheless, the proportion of CAPD patients with dyslipidemia was not significantly different between the AD and non-AD group in our study. AD was found in 58.4% among non-diabetic CAPD patients in one study, based on abnormal sympathetic skin response (SSR)[17]. However, absent SSR is dependent on the integrity of peripheral nerve or trophic skin changes, and not necessarily indicative of abnormal sympathetic function. Fifty percent of normal individuals aged >60 years could have absent plantar SSR[19].

Diabetes was an associated factor of AD by the regression analysis, and consistent with a previous study[8]. Diabetes is one of the common causes of AD from chronic hyperglycemia led to progressive autonomic neural dysfunction. The diabetes neuropathy usually begins distally and progresses proximally. The vagus nerve, which is the longest autonomic nerve, mediates approximately 75% of parasympathetic output. As such, the AD manifestation in diabetes is caused by parasympathetic denervation of vagus nerve, resulting to impaired heart rate variability[19].

Overweight[20] was also significantly associated with AD, consistent with the study of Ussawawongaraya et al.[10] illustrating that obesity might be associated with a decrease in parasympathetic function. They found an inverse association between BMI and the one-minute heart rate variability during HRVDB in CAPD patients. The proposed mechanisms were an increase in systemic sympathetic activity from insulin resistance, an increase in leptin level and non-esterified fatty acids in obese patients. Moreover, an insulin resistance in obesity could lead to desensitization of baroreflex from chronic peripheral vasodilatation. Sympathetic overactivity, parasympathetic hypoactivity and hyporesponsive baroreflex resulted in an abnormality in heart rate control and decreased heart rate variability [21-25].

There were several limitations in this study. First, we did not use the gold standard test for diagnosis of AD. Second, there was insufficient data of dialysis adequacy and ultrafiltration to determine

Table 1. Baseline characteristics comparing between AD and non-AD group (n=130).

Demographic data	AD group (n=93)	non-AD group (n=37)	p-value
Female (n, %)	40 (43.0%)	18 (48.6%)	0.565
Age (yrs) mean±SD	55.6±10.9	53.4±12.2	0.312
Age ≥65 yrs , n (%)	17 (18.3)	10 (27.0)	0.338
BMI (kg/m^2) mean±SD	23.6±3.9	21.0±3.5	**0.001**
Overweight (BMI ≥23 kg/m^2), n (%)	46 (49.5)	8 (21.6)	**0.005**
Systolic blood pressure (mmHg) mean±SD	147.3 ± 23.5	143.5 ± 21.5	0.401
Diastolic blood pressure (mmHg) mean±SD	76.9 ± 14.8	80.2 ± 13.2	0.236
Heart rate (bpm) mean±SD	75.3 ± 14.8	80.4 ± 14.0	0.072
Dialysis vintage (months), median [IQR]	33.0 [12.0-50.0]	30.0 [9.5-51.0]	0.800
Underlying disease (n, %)			
Diabetes	48 (51.6%)	10 (27.0%)	**0.012**
Hypertension	87 (93.5%)	34 (91.9%)	0.713
Dyslipidemia	71 (76.3%)	22 (59.5%)	0.084
Etiology of CKD (n, %)			
Diabetic kidney disease	41 (44.1%)	9 (24.4%)	0.204
Hypertensive nephropathy	33 (35.5%)	13 (35.1%)	
Renal calculi	13 (14.0%)	11 (29.7%)	
Glomerulonephritis	4 (4.3%)	2 (5.4%)	
Others	2 (2.1%)	2 (5.4%)	
Current medications			
Diuretics	72 (77.4%)	21 (56.8%)	0.030
ACEI or ARB*	53 (57.0%)	21 (56.8%)	1.000
Beta-blockers	56 (60.2%)	12 (32.4%)	**0.006**
Calcium channel blockers	66 (71.0%)	26 (70.3%)	1.000
Hydralazine	40 (43.0%)	13 (35.1%)	0.436
Methyldopa	13 (14.0%)	3 (8.1%)	0.555
Alpha blockers	23 (24.7%)	4 (10.8%)	0.095
Calcium carbonate	82 (88.2%)	34 (91.9%)	0.756
Vitamin D (calcitriol)	56 (60.2%)	22 (59.5%)	1.000

* ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker

Table 2 Baseline laboratory results comparing between AD and non-AD group (n=130).

Laboratory results	AD group (n=93)	non-AD group (n=37)	p-value
Hemoglobin (g/dl) mean±SD	10.5 ± 1.6	10.5 ± 1.5	0.853
Blood urea nitrogen (mg/dl) median [IQR]	49.7 [39.5-59.0]	46.0 [38.8-63.3]	0.706
Serum creatinine (mg/dl) mean±SD	9.9 ± 3.3	10.1 ± 3.2	0.700
Serum sodium (mmol/L) mean±SD	135.5 ± 4.2	136.1 ± 3.9	0.448
Serum potassium (mmol/L) mean±SD	3.9 ± 0.6	3.7 ± 0.6	**0.020**
Serum potassium <3 mmol/L, n (%)	6 (6.5%)	4 (10.8%)	0.469
Serum bicarbonate (mmol/L) mean±SD	28.0 ± 4.8	27.8 ± 4.6	0.851
Serum albumin (g/dl) mean±SD	3.6 ± 0.8	3.6 ± 0.4	0.451
Serum uric acid (mg/dl) mean±SD	6.5 ± 1.3	6.7 ± 1.2	0.356
Serum phosphate (mg/dl) mean±SD	3.9 ± 1.3	4.0 ± 1.7	0.697
Serum intact parathyroid hormone (pg/ml) median [IQR]	286 [143-450]	394 [168-490]	0.238

Table 3. The univariate and multivariate analysis of associated factors of AD in CAPD patients.

Factors	Univariate analysis			Multivariate analysis		
	odds ratio	95%CI	p-value	odds ratio	95%CI	p-value
Female	0.80	0.37 - 1.71	0.560			
Age ≥65 yrs	0.60	0.25 - 1.48	0.270			
BMI ≥23 kg/m^2	3.55	1.47 - 8.57	**0.005**	2.65	1.03 - 6.85	**0.044**
Diabetes	2.88	1.25 - 6.62	**0.013**	2.42	1.01 - 5.84	**0.049**
Hypertension	1.28	0.32 - 5.41	0.738			
Dyslipidemia	2.20	0.98 - 4.96	0.057			
Diuretics	2.61	1.16 - 5.88	**0.020**	1.93	0.80 - 4.65	0.142
ACEIs or ARBs	1.01	0.47 - 2.18	0.981			
Beta-blockers	3.15	1.41- 7.05	**0.005**	1.68	0.88 - 5.14	0.093
Calcium channel blockers	1.03	0.45 - 2.38	0.937			
Hydralazine	1.39	0.53 - 3.07	0.411			
Methyldopa	1.84	0.49 - 6.88	0.364			
Alpha blockers	2.71	0.87 - 8.47	0.086			

ACEI: angiotensin converting enzyme, ARB: angiotensin receptor blocker.

whether peritoneal dialysis contributed to autonomic dysfunction. Third, it was difficult to determine the actual dry weight of CAPD patients. The BMI in our study might have contributed to the dry weight and excess fluid. However, our study was the first research illustrating the prevalence and associated factor of AD in both diabetic and non-diabetic CAPD patients. Further study that assess dry weight or use a different measurement of adipose tissue might be better to demonstrate the association between BMI and AD. Furthermore, an evaluation of adverse outcomes and mortality in patients who had AD might have benefit to determine the importance of this condition in CAPD patients.

Conclusion

The prevalence of AD in peritoneal dialysis patients was 71.5%. Overweight and diabetes were significant associated factors.

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