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Are calcium channel blockers related to lung cancer?

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ABSTRACT

Background: Calcium channel blocker (CCB) is a common antihypertensive agent for the treatment of hypertension. There are inconsistent data of an association of CCB and lung cancer in the literature. This study aimed to evaluate this association by a case-control design.

Methods: The inclusion criteria were adult patients 18 years or over, diagnosed with hypertension, lung cancer or pulmonary tuberculosis, and presenting with one of the suggestive symptoms of lung cancer. Those who were pregnant or had a diagnosis of lung cancer or pulmonary tuberculosis prior to the diagnosis of hypertension were excluded. Diagnosis of lung cancer was made pathologically, while tuberculosis was made by positive acid-fast bacilli on sputum examination, sputum culture positive for *Mycobacterium tuberculosis*, or polymerase chain reaction positive for *M. tuberculosis* with a chest x-ray compatible with tuberculosis. Cases were those diagnosed with lung cancer, while controls were those diagnosed with tuberculosis. Factors associated with lung cancer were calculated by logistic regression analysis.

Results: There were 178 patients who met the study criteria. Of those, 69 patients (38.8%) were in the case group. The lung cancer group had *EGFR* gene mutation in 21 patients (52.5%) and adenocarcinoma was the most common cell type of lung cancer (55 patients; 79.7%). There were two factors independently associated with lung cancer including dyslipidemia and family history of lung cancer.

Conclusions: CCB was not associated with lung cancer in patients with hypertension but dyslipidemia and family history of lung cancer were independently associated with lung cancer in this setting.

Keywords: Dyslipidemia, Family history, Risk factors

Introduction

Hypertension is a common disease, with an estimated 1.39 billion adults diagnosed with hypertension (1). Generally, the prevalence of hypertension was 31.1% worldwide in 2010. The main goal of hypertension treatment is to achieve blood pressure control. A previous report found that only 23% of women and 18% of men with hypertension had a good blood pressure control globally (2). Blood pressure lowering may result in reduction of stroke by up to 40%, and reduction in heart failure by up to 50% (3). Additionally, treatment of conditions or comorbid diseases of hypertension is also crucial (4-8).

Antihypertensive agents are effective in blood pressure lowering including calcium channel blockers (CCBs). Even though CCB is recommended as the first-line treatment for hypertension (9), it has been reported to be increasing the risk of cancer (10). Several studies including a meta-analysis showed that CCB was associated with lung cancer with adjusted odds ratio of 1.13 (95% confidence interval 1.06, 1.21) (11-13), while other studies did not find this association (14,15). As there are inconsistent and inconclusive data on this issue, this study aimed to evaluate the additional association of CCB and lung cancer.

Methods

This was a case-control study conducted at Srinagarind Hospital, Khon Kaen University, Thailand. The inclusion criteria were adult patients 18 years or over, diagnosed with lung cancer or pulmonary tuberculosis, and presenting with one of the following symptoms: hemoptysis, chronic cough, constitutional symptoms, lung mass, and a checkup. Those who were pregnant or with diagnosis of lung cancer

or pulmonary tuberculosis prior to the diagnosis of hypertension were excluded. Diagnosis of lung cancer was made pathologically, while tuberculosis was made by positive acid-fast bacilli on sputum examination, sputum culture positive for *Mycobacterium tuberculosis*, or polymerase chain reaction (PCR) positive for *M. tuberculosis* with a chest x-ray compatible with tuberculosis. Cases were those diagnosed with lung cancer, while controls were those diagnosed with tuberculosis. The study period was between 2007 and 2019.

Eligible patients were recorded for baseline characteristics, medications, and risk factors for lung cancer. Baseline characteristics included age, sex, body mass index, comorbid diseases, alcohol consumption, and smoking history. Risk factors of lung cancer were also recorded: family history of lung cancer, occupational exposure, or chest wall radiation. Antihypertensive medications particularly CCB were retrieved as well as duration of CCB use. The primary outcome of this study was to evaluate the association of lung cancer and CCB.

Sample size calculation

Based on a probability of event in the case and control group of 0.6 and 0.3, the required sample size for case group was 49 patients with a confidence of 95% and power of 80%. The control group was enrolled for a ratio of case:control of 1:1-2.

Statistical analyses

Patients were categorized into two groups: lung cancer (cases) and tuberculosis (controls). Descriptive statistics were used to compare differences between both groups: independent t-test or Wilcoxon rank sum test for numerical variables and chi-square or Fisher's exact test for categorical variables. Factors associated with lung cancer were calculated by logistic regression analysis. Multicollinearity was checked in the logistic regression analysis. The final model was executed for goodness of fit by Hosmer-Lemeshow test. Statistical analyses were calculated by STATA software version 10.1 (College Station, Texas, USA).

Results

There were 178 patients who met the study criteria. Of those, 69 patients (38.8%) were in the case group or lung cancer group. The lung cancer group had tested for gene mutation in 40 patients (56.0%). *EGFR* was the most common gene mutation (21 patients; 52.5%), followed by no mutation (15 patients; 37.5%), and *ALK* mutation (4 patients; 10%). Adenocarcinoma was the most common cell type of lung cancer (55 patients; 79.7%), followed by squamous cell carcinoma (8 patients; 11.6%). Table I shows baseline characteristics and CCB treatment of the case and control groups. There were three significant factors between both groups, namely dyslipidemia, obstructive sleep apnea, and family history of lung cancer. The case group had significantly higher proportions of these three factors than the control group such as family history of lung cancer (15.9% vs. 0.9%; p < 0.001).

TABLE I - Baseline characteristics and CCB treatment of patients with hypertension categorized by lung cancer (case group) and tuberculosis (control group)

Factors	Cases (n = 69)	Controls (n = 109)	p value
Age, years*	67 (61,71)	66 (59,71)	0.603
Male	44 (63.8)	77 (70.6)	0.338
Female	25 (36.2)	32 (29.4)	
BMI			0.676
<19	13 (18.8)	17 (15.9)	
19-24.5	16 (23.2)	25 (23.4)	
24.5-30	5 (7.2)	4 (3.7)	
>30	35 (50.7)	61 (57.0)	
Smoking	40 (58)	64 (58.7)	0.922
Alcohol drinking	28 (40.6)	53 (48.6)	0.294
Comorbidities			
CVD	10 (14.5)	17(15.6)	0.841
Dyslipidemia	29 (42)	27 (24.8)	0.016
DM	27 (39.1)	48 (44)	0.518
OSA	5 (7.2)	1 (0.9)	0.033
CKD	10 (14.5)	23 (21.1)	0.269
Ischemic stroke	6 (8.7)	2 (1.8)	0.057
Autoimmune	2 (2.9)	4 (3.7)	>0.999
HBV infection	2 (2.9)	3 (2.8)	>0.999
HCV infection	0	5 (4.6)	0.158
Hyperthyroidism	1 (1.4)	0	0.388
Family history of lung cancer	11 (15.9)	1 (0.9)	<0.001
Occupational exposure	1 (1.4)	2 (1.8)	>0.999
Chest wall radiation	0	0	NA
CCB used	45 (65.2)	62 (56.9)	0.268
CCB duration, years*	5 (3-10)	6 (2.8-8.2)	0.642

Data presented as number (percentage) except * indicated as median (1st-3rd quartile range).
BMI = body mass index; CCB = calcium channel blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetic mellitus; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = not available; OSA = obstructive sleep apnea.

There were five factors in the final model for prediction of lung cancer (Tab. II). Two factors were independently associated with lung cancer including dyslipidemia and family history of lung cancer. These factors had an adjusted odds ratio (95% confidence interval) of 2.12 (1.07, 4.23) and 22.43 (2.76, 182.36), respectively. The Hosmer-Lemeshow chi-square was 4.88 (p = 0.559). CCB use had an adjusted odds ratio of 1.50 (95% confidence interval of 0.53, 2.01).

Discussion

This study found that CCB was not associated with lung cancer but dyslipidemia and family history of lung cancer did.

TABLE II - Factors associated with lung cancer in patients with hypertension by logistic regression analysis

Factors	Unadjusted OR	95% CI	Adjusted OR	95% CI
Smoking	0.97	0.53, 1.79	1.03	0.53, 2.01
Dyslipidemia	2.20	1.15, 4.20	2.12	1.07, 4.23
Obstructive sleep apnea	8.44	0.96, 73.84	7.50	0.79, 71.17
Family history of lung cancer	20.48	2.58, 162.61	22.43	2.76, 182.36
Calcium channel blocker used	1.42	0.76, 2.67	1.50	0.53, 2.01

CI = confidence interval; OR = odds ratio.

CCB-related cancer is still inconclusive and needs further studies to evaluate this issue (16). The possible mechanisms of CCB-related cancer include cell growth, cell proliferation, and cell apoptosis (17,18). However, some studies found that CCB may reduce risks of lung cancer as CCB may suppress lung tumorigenesis and suppression of *CACNA2D2*, a link to non–small cell lung cancer (19,20). Previous studies and meta-analyses that reported on the risk of CCB on lung cancer were mainly from database study with asymptomatic controls, while this study evaluated this association with a case-control study using controls who presented with similar symptoms of lung cancer.

Rotshild et al published one meta-analysis and one nested case-control study. Both studies reported that CCB was associated with lung cancer with an adjusted odds ratio of 1.13 (95% confidence interval 1.06, 1.21) and a risk ratio of 1.15 (95% confidence interval 1.01-1.30) (12,13). However, there are some limitations in both studies. The case-control study did not state how lung cancer diagnosis was made and significant factors in this study, namely dyslipidemia and family history of lung cancer, were not studied (12). The results of this study were compatible with the large population cohort study in Hong Kong (21). Among 84,116 patients with lung cancer, CCB did not increase the risk of lung cancer regardless of aspirin therapy. The hazard ratios for both settings were 0.89 (95% confidence interval of 0.73, 1.08) for CCB and 0.82 (95% confidence interval of 0.64, 1.06) for CCB plus aspirin. As data regarding CCB and lung cancer are still conflicting, further studies are required.

This study found that dyslipidemia was associated with lung cancer, which was supported by a previous study from China (22). High-density lipoprotein cholesterol (HDL-C) reduced the risk of non–small cell lung cancer by 77% (adjusted odds ratio of 0.233; 95% confidence interval of 0.134, 0.407). There are several biological explanations for the reduction of cancer and high HDL-C, such as suppression of signaling via lipid raft formation and reduction of viability and proliferation (23,24). Regarding family history of lung cancer, several studies support this finding conducted in twins, women, and nonsmokers (25-27). This association may be explained by second-hand smokers or genetic factors such as *HER2* gene or *EGFR* variant (28-32).

Study Limitations

There are some limitations in this study. First, this was a study conducted in a single, referral university hospital resulting in a small sample size. Second, some factors were not completely evaluated such as genetic factors, sleep apnea, or aspirin therapy (21,33-38). Similar to previous published articles, smoking history may be underestimated as smoking status may not be recorded in the medical records (12,13,21). Additionally, selection bias may have existed as this study enrolled only those with pathological diagnosis of lung cancer. This may also result in small sample size. Finally, some factors such as alcohol consumption may not be studied or may be missing due to retrospective design.

Conclusions

CCB was not associated with lung cancer in patients with hypertension but dyslipidemia and family history of lung cancer were independently associated with lung cancer in this setting.

Disclosures

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