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Association of pre-hospital theophylline use and mortality in chronic obstructive pulmonary disease patients with sepsis

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ABSTRACT

Background: Although theophylline has been shown to have anti-inflammatory effects, the therapeutic use of theophylline before sepsis is unknown. The aim of our study was to determine the effect of theophylline on COPD patients presenting with sepsis.

Methods: This nationwide, population-based, propensity score-matched analysis used data from the linked administrative databases of Taiwan's National Health Insurance program. Patients with COPD who were hospitalized for sepsis between 2000 and 2011 were divided into theophylline users and non-users. The primary outcome was 30-day mortality. The secondary outcome was in-hospital death, intensive care unit admission, and need for mechanical ventilation. Cox proportional hazard model and conditional logistic regression were used to calculate the risk between groups.

Results: A propensity score-matched cohort of 51,801 theophylline users and 51,801 non-users was included. Compared with non-users, the 30-day (HR 0.931, 95% CI 0.910–0.953), 180-day (HR 0.930, 95% CI 0.914–0.946), 365-day (HR 0.944, 95% CI 0.929–0.960) and overall mortality (HR 0.965, 95% CI 0.952–0.979) were all significantly lower in theophylline users. Additionally, the theophylline users also had lower risk of in-hospital death (OR 0.895, 95% CI 0.873–0.918) and need for mechanical ventilation (OR 0.972, 95% CI 0.949–0.997).

Conclusions: Theophylline use is associated with a lower risk of sepsis-related mortality in COPD patients. Pre-hospital theophylline use may be protective to COPD patients with sepsis.

1. Introduction

According to the third international consensus definitions, sepsis is newly defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. In the United States, the annual incidence increased from 8.7% in 1979–2000 to 13.3% in 2004–2009 [2], and this rise have caused a huge economic burden [3,4]. In Taiwan, sepsis is the eleventh

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leading cause of death and a major cause of admission. The annual incidence rates increased by 1.6-fold with an annual percent change of 3.9% [5]. Along with international guidelines for the management of severe sepsis and septic shock [6], the implementation of early resuscitation and management bundles seemed to have contributed to the decrease in mortality over the past few decades [7]. However, despite national as well as international consensus statements regarding the primary therapeutic goals and guidelines for the management of sepsis, the hospital mortality rate of sepsis and septic shock varied significantly between different geographic regions of the world. Compliance with all of the evidence-based bundle metrics for the treatment of this condition was not high. Wide differences remain between hospitals in the delivery of care for patients with sepsis.

The explanations regarding the onset and progression of sepsis mainly focuses on a series of inflammatory responses, including release of proinflammatory mediators initiating a chain of reactions that lead to widespread organ dysfunction [8]. It is therefore, no surprise, that investigations into therapeutic agents, which could potentially modulate inflammatory responses in septic patients, are an area of active research.

Theophylline, a dimethylxanthine, has been used in the treatment of asthma and chronic obstructive pulmonary disease (COPD) for more than 70 years [9]. It was originally used as a bronchodilator; however, the relatively high frequency of side effects and its narrow therapeutic range limited widespread use. More recently, there is renewed interest in theophylline as therapeutic agent in critically ill patients, since it has been shown to have anti-inflammatory effects at low concentrations [10].

As such, we hypothesize that theophylline may be a potential therapeutic agent in the treatment of sepsis by targeting a number of inflammatory and immune modulating pathways involved in the development and/or propagation of sepsis. Therefore, we conducted a large-scale, population-based, propensity score–matched study to investigate the association of pre-hospital theophylline use and mortality after hospital admission for sepsis in Taiwanese COPD patients.

2. Material and methods

2.1. Data source

The Taiwan National Health Insurance Research Database (NHIRD) was used to abstract data for analysis in the current study. The detailed information of this database was described in the previous studies [11,12]. Briefly, NHIRD contains de-identified secondary healthcare-related data related to 99.9% of the 23 million residents of Taiwan. This database includes information related to all outpatient, inpatient, emergency, dental, and traditional Chinese medicine services, as well as detailed records of prescription drugs usage. Diseases are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; 2001 edition). The accuracy of diagnosis of sepsis was validated in our previous study according to The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [13]. The accuracy was 92.3% in our 340 randomly selected inpatients ($\kappa = 0.806$; 95% confidence interval, 0.799–0.813) [12]. The accuracy of diagnoses recorded in the NHIRD has been validated for several diseases [11]. The study protocol was approved by the Taipei City Hospital Research Ethics Committee.

2.2. Study design and data collection

In this nationwide population-based cohort study in Taiwan, our goal was to investigate the association between pre-hospital theophylline use and subsequent mortality in COPD patients hospitalized with sepsis. We included all COPD patients with an index hospitalization for sepsis between January 2000 and December 2010. The diagnosis of sepsis was validated in our previous study [12]. The index date was defined as the first day of hospitalization for sepsis and all subjects were followed until death, or end of 2011, whichever came first.

2.3. Exposure to theophylline and other drugs

We identified all drug prescriptions before the index date. Theophylline use was defined as the presence of an active theophylline prescription within 30 days before the index date. According to the World Health Organization Anatomical Therapeutic Chemical Classification System [14], drugs for obstructive pulmonary disease were categorized as following: 1) inhaled adrenergics or anticholinergics; 2) inhaled glucocorticoids; 3) systemic steroid; 4) systemic adrenergics; and 5) others. Others include leukotriene receptor antagonists (ATC code R03DC) and other systemic drugs for obstructive airway diseases (ATC code R03DX). We also identified patients' use of medications that would potentially confound the association between theophylline use and sepsis outcomes, such as antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), beta blockers, calcium-channel blockers, proton-pump inhibitors, anti-hyperglycemic drugs, and antidepressants.

2.4. Sociodemographic characteristics and comorbidities

Baseline sociodemographic characteristics, such as age, sex, monthly income (<NT$19,100, NT$19,100–41,999, and ≥NT$42,000), and level of urbanization, were recorded. The cut-off values for monthly income were according to the monthly minimum wage of workers legally defined by the Taiwan government and the mean monthly income. We have used these cut-off values in previous studies [15,16] Urbanization levels were classified according to the system used in National Health Research Institutes publications, which ranges from level 1 (most urban) to level 4 (least urban) [17]. The Charlson Comorbidity Index (CCI) was used to determine individuals' overall health status before hospital admission, with each increase in the CCI score representing a stepwise increase in cumulative mortality [18]. We categorized the cause of sepsis according to infection site (respiratory tract, bacteremia, genitourinary tract, intra-abdominal, wound, central nervous system, device-related, endocarditis, and other). Information related to systemic diseases not included in the CCI, such as history of chronic arrhythmia, coronary artery disease, hypertension, dyslipidemia, and major surgery, were also abstracted from the NHIRD.

2.5. Propensity score matching

In the current study, we performed 1:1 propensity score-matching analysis. Using matching according propensity score reduced the confounding from measured variables in the