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Research Article

Antipsychotics-Associated Venous Thromboembolism in Intensive Care Unit: A Prospective Cohort Study

Ahmed Al Rashed[1]; Isamme Al Fayyad[2]; Mohamad Al-Tannir[2]

[1]Pharmacy Administration, King Fahad Medical City, Riyadh Second Health Cluster, Riyadh, Saudi Arabia

[2]Research Center, King Fahad Medical City, Riyadh Second Health Cluster, Riyadh, Saudi Arabia

***Corresponding author:** Mohamad Al-Tannir, Research Center, King Fahad Medical City, Riyadh Second Health Cluster, Riyadh, Saudi Arabia.

Email: maltannir@kfmc.med.sa

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Abstract

Background: Studies have shown that antipsychotic drugs use may lead to venous thromboembolisms (VTEs); however, this association has not been established in patients admitted to intensive care unit (ICU).

Objectives: The aim of this study is to determine the relationship between antipsychotic agents and development of VTE in critically ill patients during ICU admission.

Materials and Methods: This cohort study, conducted between June 2019 and December 2021, was based on a prospectively collected database of critically ill adult patients admitted to ICU. The primary outcome was defined as incidence of VTE, either deep venous thrombosis (DVT) or pulmonary embolism (PE). All included patients were followed-up for VTE development from the time of ICU admission until patient discharge, transfer from ICU, death, and discontinued antipsychotic medications. The confounding risk factors of all-cause VTE were assessed as the secondary outcome. A multivariable Cox proportional hazards model was developed to adjust for measured confounding risks.

Results: A total of 274 patients were included in the study (137 in each group). The incidence rate of VTE was 1.5% in antipsychotics users while no cases DVT were developed in non-antipsychotics users. The antipsychotic users were 2.54-fold more likely to die than the non-psychotic users (p=0.012). Multivariate analysis showed no significant increased risk of death associated with antipsychotic exposure in both groups.

Conclusions: In this cohort study, exposure to antipsychotic drugs was not found to be associated with an increased risk of VTE among patients and who discontinued anticoagulation. Further studies are warranted to confirm these findings.

Keywords: Venous thromboembolism; Pulmonary embolism; Deep vein thrombosis Antipsychotic agents; Cohort study; Intensive care Unit

Introduction

Venous Thromboembolism (VTE), which involves Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), is a common disease and a leading cause of patient morbidity and death [1]. VTE is frequently encountered in patients admitted to Intensive Care Unit (ICU) as high as 81% in critically ill patients not treated with thromboprophylaxis based and by 44% in critically ill patients managed with thromboprophylaxis [2]. Although it is treatable, VTE has potential fatal risks and estimates to contribute in mortality by 30% if not treated and by 2-8% if treated [3-6]. A meta-analysis illustrated that DVT patients have longer hospital stay 11.2 days (95% CI: 3.82–18.63 days; p=0.003) and mechanical ventilation 4.85 days (95% CI: 2.07–7.63) compared to non-DVT patients [7]. The cost of PE hospitalization estimated to be $8,764 and annual health plan payments of VTE service elevated to the average of $15,123 [8].

Several potential risk factors increase the risk of VTE among ICU patients', including history of VTE, postoperative status and active malignancy, mechanical ventilation, immobility, femoral venous catheters, emergency surgery, APACHE II score, platelet count >450x10^9/L, and medications such as sedatives and paralytic agents [9]. Other risk factors include age, immobilization, obesity, respiratory or heart failure, and pregnancy [10-13].

Numerous studies have suggested that antipsychotic drugs could be associated with an increased risk for a first episode of VTE [14,15]. It is recognized that antipsychotics have various adverse effects with most attention has been paid to metabolic adverse effect such as obesity, dyslipidemia, diabetes mellitus and hyperleptinemia especially with Second Generation Antipsychotics (SGA) or extrapyramidal syndrome and tardive dyskinesia particularly with First Generation Antipsychotics (FGA) and less attention has been paid to VTE [6,16,17]. Antipsychotics initiated in ICU admitted patients for the purpose of controlling acute psychosis, substance withdrawal, agitation and delirium [18,19]. The most frequently agents used for delirium in ICU was haloperidol (62) followed by quetiapine (31%), risperidone (15%;), olanzapine (13%), ziprasidone (4%), aripiprazole (3%), clozapine (0.4%), and paliperidone (0.2%) [20]. There are several proposed mechanisms behind antipsychotics

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induced VTE. First explanation is elevation of prolactin level resulting in platelet activation and platelet aggregation. Second mechanism is elevation of antiphospholipid antibodies, including anticoagulants and anticardiolipin antibodies which are associated with increased risk of venous or arterial thrombosis. Third elucidation is sedative effect caused by antipsychotics especially low-potency antipsychotic drugs resulting in immobility and its link to venous stasis and exacerbating the risk of VTE [21-24].

A recent meta-analysis (2021) of antipsychotic agent uses and risk of VTE that included 28 observational studies demonstrated that antipsychotic users have significantly increased risks of VTE [OR 1.55; 95% CI: 1.36-1.76] and PE (OR 3.68; 95% CI: 1.23-11.05) compared to non-users. Moreover, subgroup analyses suggested that new users are more likely to develop VTE [14]. Another recent meta-analysis (2021) has investigated the use of antipsychotic and Risk of VTE and included 22 studies showed that antipsychotic usage can increase the risk of VTE. Young people are at a higher risk of VTE than elderly when taking antipsychotic [15].

Since then, several studies have reported a rise in antipsychotics induced VTE, and attention is paid to assess this risk in specific population such as ICU patients taking antipsychotics and whether they increase the risk of VTE during ICU admission. There is no study evaluating the relationship between VTE and use of antipsychotics during only ICU admission. Hence, we aimed in this study to estimate the risk of VTE in association with antipsychotic drugs among ICU hospitalized patients.

Materials and Methods

Study Designs and Settings

A prospective cohort study was conducted at the ICU of King Fahad Medical City. All consecutive patients aged 18 and over seen between June 2019 and December 2021 were enrolled in the study. Diagnosis of DVT was confirmed by a formal report showing the absence of full compressibility of proximal or distal vein of the lower limb on ultrasonography, and the diagnosis of PE was established chest computed tomography scan. All patients were treated in accordance with the institution standards of care.

Inclusion Criteria: All patients who meet the following criteria:

a) Patients (age ≥ 18 years old) who are diagnosed with a first unprovoked VTE event were included in the study. Firs unprovoked VTE event defined as VTE diagnosed in the absence of surgery or plaster cast, pregnancy or post-partum in the 3 months prior to the index VTE event, VTE not associated with contraception or hormone replacement therapy, and non-caner associated VTE. Diagnose of VTE is confirmed by Compression Ultrasonography (CUS) with Doppler of lower extremities. Diagnosis of Pulmonary embolism is established by Computed Tomography Pulmonary Angiography (CTPA) or combination of high pre-test clinical probability of PE with high probability ventilation–perfusion (V/Q) lung scan

b) The patients had no indication for indefinite anticoagulation (e.g. atrial fibrillation or recurrent VTE while on anticoagulation or major thrombophilia)

c) Patients new started on antipsychotic treatment (typical and atypical) during ICU admission for controlling delirium, agitation, acute psychosis, or substance withdrawal.

Exclusion Criteria

a) Patients who have history allergy to any antipsychotics.

b) Patients who are administered antipsychotics for chronic use such as schizophrenia or bipolar disorder prior ICU admission

c) Pregnant women

Drug Exposure

All medications used before to the VTE index event were gathered at inclusion. Drugs frequently consumed before admission but stopped taking more than a week before to admission were not noted. At every visit or interaction during the follow-up, data on drug exposure was gathered. We assessed the exposure to antipsychotic drugs after the end of anticoagulation treatment and until patient discharge, transfer from ICU, death, and discontinued antipsychotic medications.

Study outcomes and Follow up

The study outcomes included three parts. Part one assessed the demographic characteristics and Confounding risk factors:(e.g. history of VTE, history of cancer, post-surgery, mechanical ventilation, APACHE score, patients on sedative agent or paralytic agents). The second part captured the antipsychotic treatment (categorized into conventional (typical) and atypical agents), and the name of antipsychotic agent, total dose per day, and duration of antipsychotics (it is counted from first date and last days of antipsychotics administration to calculate the duration of drug exposure). The third part described the type of VTE, whether DVT or PE.

If no antipsychotic medications were prescribed to the patient throughout the follow-up, we classed them as non-users. After the anticoagulant therapy was finished, exposure was defined as receiving at least one prescription for an antipsychotic medication. As a result, exposure to antipsychotic medications includes both instances of therapy continuation (current users) and new antipsychotic medication users during follow-up. To determine the length of drug exposure, we noted the calendar dates of the first and last days of drug consumption.

Sample Size Calculation

With an expected incidence of 32% in the non-antipsychotic users and assumed relative risk of 2.99 for VTE development, 0.95 confidence interval, and a desired 0.8 power, we need a total of 276 patients. 138 patients in the exposed group (case: antipsychotic users) and 138 in the non-exposed group (control: non-antipsychotic users).

Statistical Analysis Plan

Demographic and clinical characteristics and study outcomes were summarized using descriptive statistics (frequency, percentage) for categorical data and mean (Standard Deviation [SD]) for continuous data where appropriate. We compared between antipsychotic drug users and non-users of antipsychotic drugs using the Chi-square or Fisher's exact tests for categorical variables, and Student t-test/Mann-Whitney for continuous variables where appropriate. Survival analysis was used to analyze the association between antipsychotic drugs exposure and the risk of VTE development. Probability of mortality

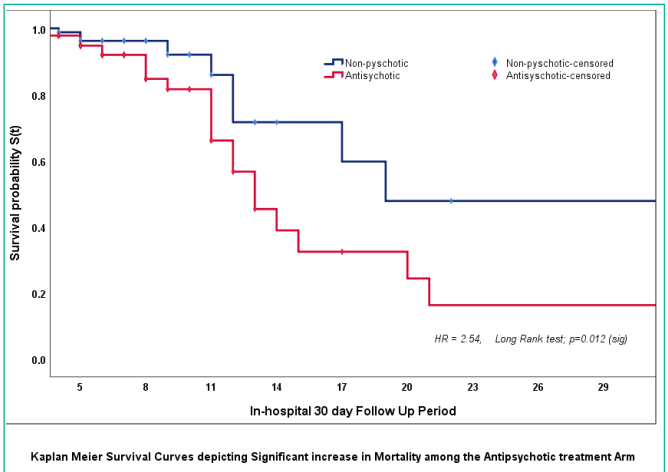

Figure 1: Cumulative probability of mortality.

was assessed using the Kaplan-Meier method, and multivariate cox proportional hazard regression was used to identify the confounders between antipsychotic drug use and the risk of mortality. Variables significant to $p < 0.05$ will be retained into the final analysis model. Hazard ratios with their 95% confidence interval were calculated and reported.

Ethical Consideration

The study proposal was reviewed and approved by the institutional review board of King Fahad Medical City prior to the study conduct. Patient's identities were anonymized. Informed consent was waived as the study does not include any risk.

Results

Study participants' characteristics are shown in Table 1. A total of 274 patients were included in the study (137 patients in each group). The mean age for the study and control groups was 53±17 and 54±16 respectively. Mean body mass index was higher in the control group 26.9 ± 4.8 kg/m^2 (p=0.013). History of VTE was present in one case in the control group. The majority of patients in study groups were hypertensive, diabetic, and post-operative. Moreover, 95.6% of the study group were on mechanical ventilator compared to 78.1% in the control group. APACHE scores were almost equal between the study groups. Slightly more three-quarters of study participants were on Enoxaparin. About 40.9% in the study group compared to 45.9% in the control groups were on Midazolam (Table 1).

During follow-up, a total of 2 of the 274 patients (1.5%) had developed VTE (DVT). During follow-up, 34 deaths were reported: 25 (18.2%) among antipsychotics users as compared with 9 (6.6%) among non-users (p=0.009).

The cumulative probability of mortality was different between users and non-users of antipsychotics (Log-rank, p = 0.012) (Figure 1). The antipsychotic users were 2.54 (Hazard Risk (HR)) fold more likely to die than the non-psychotic users (p=0.012).

Multivariate analysis showed no significant increased risk of death associated with antipsychotic exposure in both groups.

Table 2: Follow up of the total cohort and comparison between users and non-users of antipsychotic drugs.

Characteristic	Control group Non users of antipsychotics (n = 137)	Study group users of antipsychotics (n = 137)
Incidence rate of VTE (Only DVT)	0	2 (1.5%)
Death during the follow-up	9 (6.6%)	25 (18.2%)

Table 1: Baseline characteristics of the 274 patients according to the use or not of antipsychotic drugs during follow-up.

Characteristic	Description	Control group Non users of antipsychotics (n = 137)	Study group users of antipsychotics (n = 137)	p value
Age (year)	Mean ± SD	54±16	53±17	0.784
Gender	Male	80 (58.4)	99 (72.3%)	0.016
BMI (Kg/m^2)	Mean ± SD	26.9 ± 4.8	25.6 ± 3.3	0.013
History of VTE	n (%)	1 (0.7%)	0	0.316
History of Hypertension	n (%)	100 (73%)	123 (89.8%)	<0.001
History of diabetes mellitus	n (%)	98 (71.5%)	122 (89.1%)	<0.001
History of Cancer	n (%)	4 (2.9%)	3 (2.2%)	0.702
Post-surgery	n (%)	80 (58.8%)	99 (72.3%)	0.019
Mechanical ventilation	n (%)	107 (78.1%)	131 (95.6%)	<0.001
APACHE score	Mean ± SD	29 ± 6	29 ± 4	0.866
Vascular Access Devices	n (%)	114 (83.2%)	135 (98.5%)	<0.001
Platelet count	Mean ± SD	248 ± 94	254 ± 97	0.578
Current VTE prophylaxis	Heparin	33 (24.1%)	32 (23.4%)	0.887
	Enoxaparin n (%)	104 (75.9%)	105 (76.6%)	
Sedative agent	n (%)	61 (44.5%)	56 (40.9%)	0.541
Name of sedative agent	Midazolam n (%)	28 (45.9%)	34 (60.7%)	0.114
	Precedex n (%)	15 (24.6%)	6 (10.7%)	
	Propofol n (%)	18 (29.5%)	16 (28.6%)	
Paralytic agent	Nimbex	4 (2.9%)	0	0.044
Length of hospital stay	Mean ± SD	7 ± 9	7 ± 5	0.895

Table 3: Hazard ratios for the risk of death in univariate and multivariate analyses.

	Non-antipsychotic users				Antipsychotic users			
	Unadjusted HR (95% CI)	p value	Multivariate HR (95% CI)	p value	Unadjusted HR (95% CI)	p value	Multivariate HR (95% CI)	p value
Age (year)	1.01 (0.96 - 1.06)	0.751	1.01 (0.96 - 1.07)	0.694	1 (0.98 - 1.02)	0.922	1.01 (0.99 - 1.03)	0.465
Gender (Male)	2.67 (0.64 - 11.17)	0.180	2.77 (0.52 - 14.74)	0.233	2.06 (0.8 - 5.33)	0.135	2.41 (0.85 - 6.84)	0.098
BMI	0.99 (0.87 - 1.12)	0.821	1.02 (0.86 - 1.2)	0.861	1.03 (0.93 - 1.14)	0.579	1.02 (0.9 - 1.16)	0.746
APACHE score	1.03 (0.91 - 1.16)	0.652	1.02 (0.89 - 1.18)	0.750	0.94 (0.86 - 1.01)	0.098	0.95 (0.87 - 1.04)	0.246
History of Hypertension	3.08 (0.38 - 25.02)	0.292	3.13 (0.12 - 78.49)	0.488	2.6 (0.75 - 8.97)	0.130	0.94 (0.16 - 5.44)	0.942
History of diabetes mellitus	2.19 (0.45 - 10.61)	0.330	0.76 (0.07 - 8.55)	0.821	5.96 (0.8 - 44.45)	0.082	5.6 (0.38 - 82.46)	0.209
Post-surgery	1.09 (0.27 - 4.42)	0.900	1.27 (0.29 - 5.56)	0.753	0.87 (0.37 - 2.08)	0.759	0.67 (0.27 - 1.68)	0.395

Discussion

In this cohort-study of patients exposed to antipsychotic drugs after anticoagulation discontinuation have a risk of VTE of 1.5%. Antipsychotic drug exposure was associated with an increased risk for death. The relationship between antipsychotic drugs and VTE was discovered as early as 1950s [25]. Since then, several epidemiological case-control and cohort studies have reported the relationship between antipsychotic drugs and VTE. Many observational and meta-analysis studies have showed a positive association between antipsychotic drugs usage and VTE risk with a wide range (from 1.17 to 13.30) [14,15,26-28].

Yet, the biological mechanism of VTE induced by antipsychotic drugs is not clear, nonetheless a number of hypotheses have been proposed, such as obesity, sedation, hyperprolactinaemia, hyperhomocysteinaemia, antiphospholipid antibodies and aggregation of platelets induced by antipsychotic drugs [26,30]. Additionally, critically ill patients are at high risk of developing venous VTE during their hospitalization in the ICU because of the presence of several risk factors [31]. The prevalence of developing VTE during the ICU ranges from 8% to 40%. However, there is a scarcity in the literature reporting the risk of critically ill users of antipsychotic drugs in the ICU.

The risk of VTE in this study is similar to the pooled odd ratio 1.55 (95% CI: 1.36-1.76) of the meta-analysis study of Liu et al., (2021), indicating a significant increased risk of VTE in antipsychotic drugs users compared with non-users [14]. Moreover, the results of another systematic review reported by Di et al., showed that exposure to antipsychotic drugs increased the risk of VTE 1.53 (95% CI:1.33-1.77) (2020), which is consistent with our study findings [15]. Another meta-analysis reported in 2014 the association between antipsychotic drugs use and the risk of VTE and their findings are consistent with ours [32]. Due to the high heterogeneity among the included studies in those systematic meta-analyses studies, definitive conclusions cannot be drawn, these results warrant the clinicians to be cautious when using certain antipsychotic drugs.

The hazard ratio of death in this study were more than two-fold among the antipsychotic drugs users compared with non-users. Which is less than the mortality reported in a previous study investigated the impact of antipsychotic drugs on mortality in people with Parkinson disease (4.20, 95% CI 2.13-7.96) [33]. Another national case-control study examined the association between the use of antipsychotic drugs and fatal PE had showed 13-fold risk of death from PE [28]. In contrast, a Cohort Study evaluated the impact of Antipsychotic drugs on VTE showed a HR of 1.63 (95% CI, 1.26-2.10) [34], which is lower than our reported HR.

To the best of our knowledge, this prospective cohort study is the first to assess the risk of VTE associated with antipsychotics exposure in critically ill patients hospitalized in the ICU. However, our study has also some limitations. Although we to addressed many potential confounders, residual confounding is always possible, such as immobilization or inflammation cannot be ruled out. The number of people treated with concurrent antipsychotics is modest.

Conclusion

This was the first study assessing the risk of VTE associated with antipsychotic drugs among critically ill patients from Saudi Arabia. The current study indicates that a significant increased VTE risk was found in current antipsychotic drugs users compared with non-users. The clinical impact on the management of VTE should be considered into account, in particular the duration of anticoagulant treatment, therefore, larger studies are needed among critically ill users' antipsychotic drugs of to confirm or refute our results, and further explore the possible association between antipsychotic drugs usage and death rate.

Authors Statements

Study Design

AR and MT; methodology, AR, MT and IF; data collection, AR; data analysis, IF and MT and IF; writing-review and editing, AR, MT and IF; All authors have approved the final version of the manuscript for submission.

Conflict of Interests

All authors declare that they have no conflict of interest.

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