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A NESTED CASE-CONTROL STUDY ON ANTIPSYCHOTIC DRUGS AND RISK OF VENOUS THROMBOEMBOLISM AMONG MENTALLY ILL PATIENTS

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ABSTRACT

Context: There is an association between use of antipsychotic drugs and risk of venous thromboembolism in a large primary care population. The increased risk was more marked among new users and those prescribed atypical antipsychotic drugs. **Aim of the study:** To determine association between antipsychotic drugs and risk of venous thromboembolism in nested cases and controls. **Methods:** After obtaining implied consent, mentally ill cases and controls with & without record of venous thromboembolism between January 2014 and December 2016, who fulfilled the inclusion criteria were enrolled in the study through computerized codes/Medical records patients in Government Head Quarters Hospital at Erode. Each case with venous thromboembolism matched with up-to two controls without venous thromboembolism (50 cases and 100 matched controls) by adapting propensity matching were recruited during April 2017. Incidence density sampling technique was used to recruit the nested cases and controls among mentally ill patients based on the detection of the cases, controls were selected and matched. **Results:** The computed odds ratio between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls showed statistical significance with current timing of antipsychotic use, both typical & atypical antipsychotics, low and high potency of antipsychotics & oral mode of drug administration. Significant association ($\chi 2$= 5.64) was obtained between risk of venous thromboembolism and diagnosis in controls. **Conclusion:** Psychiatric nurses should be hyper vigilant to identify the antipsychotic drugs and risk of venous thromboembolism among mentally ill patients in clinical settings.

KEYWORDS: Antipsychotics, Venous Thromboembolism, Nested- Case Control, Mentally Ill.

INTRODUCTION

Antipsychotic medications are mainstays in the treatment of schizophrenia and a range of other psychotic disorders.[1] Antipsychotic medications are primarily indicated for the treatment of schizophrenia and other psychotic disorders [including schizoaffective disorder, delusional disorder and bipolar affective disorder (BPAD)]. They have traditionally been categorized as first-generation (formerly known as 'typical' or 'conventional') antipsychotics (FGAs) or second-generation antipsychotics (SGAs) (formerly 'atypical' antipsychotics).[2] Venous thromboembolism has been associated with antipsychotic drugs, but the underlying mechanisms are largely unknown. Increased plasma levels of prolactin should probably be taken into account during the monitoring of antipsychotic treatment as well as in future research concerning venous thromboembolism in psychiatric settings.[3]

Venous thromboembolism (VTE) is a common condition, with an annual incidence of more than 1 per 1000 persons.[4] Recent research has focused on increased risk for VTE in psychiatric settings.[5] More recent literature has also found an association between other second-generation antipsychotics and elevated risk for VTE.[6] The risk of VTE with typical and atypical antipsychotics varies with type of drug and is highest just after starting the drug.[7] Paucity of research literature on antipsychotic drugs and risk of venous thromboembolism with nested case-control study initiated the investigator to conduct the present study. The novelty of the research work is on antipsychotic drugs and risk of venous thromboembolism - nested case-control study, in which each case matched with up-to two controls.

MATERIALS AND METHODS

After obtaining implied consent, mentally ill cases and controls with & without record of venous thromboembolism between January 2014 and December

2016, who fulfilled the inclusion criteria were enrolled in the study through computerized codes/Medical records patients in Government Head Quarters Hospital at Erode. Each case with venous thromboembolism matched with up-to two controls without venous thromboembolism (50 cases and 100 matched controls) by adapting propensity matching were recruited during April 2017. Incidence density sampling technique was used to recruit the nested cases and controls among mentally ill patients based on the detection of the cases, controls were selected and matched. Demographic profiles like age, gender, BMI & diagnosis were also recorded.

Statistical methods adopted were multiple conditional logistic regressions to estimate the Odds Ratio (with 95% confidence interval), estimation of Risk ratio, Cox Hazard ratio & Number Needed to Treat (NNT) and non parametric, Chi square test to estimate the association between risk of venous thromboembolism and the selected demographic profiles. A probability of 0.05 or less was taken as statistically significant. Statistical package for social science, PCT version 17(SPSS Inc, Chicago) was used for analyzing the data.

RESULTS

Demographic profile according to the age group delineates that highest percentage (40%) were between 51-60 years among cases, whereas majorities 45% were between 51-60 years among controls. Gender depicts that paramount 60% & 57% were males among nested cases and controls respectively. According to BMI, highest percentages (50%) were obese in cases; however 47% had overweight in controls. Demographic profile according to the diagnosis revealed that majority 40% have been diagnosed with schizophrenia in cases, whereas 42% were diagnosed with BPAD in controls (Table 1).

Table 1: Frequency and percentage distribution of demographic profile among nested cases and controls.

S.No	Demographic Profile	Categories	Cases		Controls	
			N_1 50	%	N_2 100	%
1	Age	20-40 years	16	32	20	20
		41-50 years	14	28	35	35
		51-60 years	20	40	45	45
2	Gender	Male	30	60	57	57
		Female	20	40	43	43
3	BMI	Underweight	10	20	32	32
		Overweight	15	30	47	47
		Obese	25	50	21	21
4	Diagnosis	Schizophrenia	20	40	35	35
		BPAD	13	26	42	42
		Dementia	17	34	23	23

Frequency and percentage distribution of timing of antipsychotic use showed that highest percentages (40% & 40%) were recent & past users respectively among cases, likewise highest percentage 42% were recent users among controls. Highest 40% of users were both typical & atypical antipsychotics in cases; however maximum 37% were typical users in controls. Frequency and percentage distribution of potency of antipsychotics portrayed that paramount 56% received high potency in cases; contradictorily highest percentage (56%) of the mentally ill patients received low potency in controls. Highest percentage (42% & 40%) received oral mode of drug administration among nested cases and controls respectively (Table 2).

Table 2: Frequency and percentage distribution of risk of venous thromboembolism in nested cases and controls.

Risk of venous thromboembolism	Cases		Controls	
	Frequency N_1 50	Percentage (%)	Frequency N_2 100	Percentage (%)
Timing of antipsychotic use				
Current (within past 3 months)	10	20	37	37
Recent (4-12 months before)	20	40	42	42
Past (13-24 months before)	20	40	31	31
Types of antipsychotic received				
Typical only	16	32	37	37
Atypical only	14	28	32	32
Both typical & atypical	20	40	31	31
Potency of antipsychotics				
Low potency	22	44	56	56
High potency	28	56	44	44
Mode of drug administration				
Oral	21	42	40	40
Intra Muscular	16	32	32	32
Intra Venous	13	26	28	28

The estimated risk ratios revealed that timing of antipsychotic use (current) were statistically significant (0.54) in cases and controls. In types of antipsychotic received, both typical & atypical were statistically significant (1.65) in cases and controls. In course of estimated risk ratio on potency of antipsychotics delineated that low and high potency were statistically significant (0.61; 1.64) in cases and controls. Oral modes of drug administration were statistically significant (1.56) in cases and controls (Table 3).

The estimated odds ratio between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls showed statistical significance (0.42) in current timing of antipsychotic use. It implied that there was 0.42 times risk of developing venous thromboembolism among mentally ill patients owing to current timing of antipsychotic usage. The computed odds ratio between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls showed statistical significance (2.27) in both typical & atypical antipsychotics. It implied that there was 2.27 times risk of developing venous thromboembolism among mentally ill patients considering both typical & atypical antipsychotics (Table 3).

The estimated odds ratio between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls showed statistical significance (0.46 & 2.05) in low and high potency of antipsychotics respectively. It signified that there was 0.46 & 2.05 times risk of developing venous thromboembolism among mentally ill patients as a result of low and high potency of drugs respectively. The computed odds ratio between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls showed marginal statistical significance (1.99) in oral mode of drug administration. It signified that there was 1.99 times risk of developing venous thromboembolism among mentally ill patients as a result of oral mode of drug administration (Table 3).

Table 3: Estimation of risk and odds ratio for the cases and controls among mentally ill patients.

Risk of venous thromboembolism	Cases & Controls		Cases & Controls	
	Risk Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Timing of antipsychotic use Current (within past 3 months)	**0.54**	**p = 0.04**	**0.42**	**p = 0.03**
Recent (4-12 months before)	0.95	p = 0.81	0.92	p = 0.81
Past (13-24 months before)	1.29	p = 0.26	1.48	p = 0.27
Types of antipsychotic received Typical only	0.86	p = 0.55	0.80	p = 0.54
Atypical only	0.87	p = 0.62	0.82	p = 0.61
Both typical & atypical	**1.65**	**p = 0.01**	**2.27**	**p = 0.01**
Potency of antipsychotics Low potency	**0.61**	**p = 0.02**	**0.46**	**p = 0.01**
High potency	**1.64**	**p = 0.03**	**2.05**	**p = 0.03**
Mode of drug administration Oral	**1.56**	**p = 0.04**	**1.99**	**p = 0.05**
Intra Muscular	1.00	p = 1.00	1.00	p = 1.00
Intra Venous	0.64	p = 0.10	0.52	p = 0.09

The estimated cox Hazard Ratio portrayed that 2 cases demised due to high potency of antipsychotics and 1 subject from controls demised due to the administration of both typical and atypical antipsychotics related with the risk of venous thromboembolism. The estimated value of Number Needed to Treat (NNT) on risk of venous thromboembolism among cases and controls delineated that 6 mentally ill patients out of 50 in cases & 100 in controls should be treated (Fig 1).

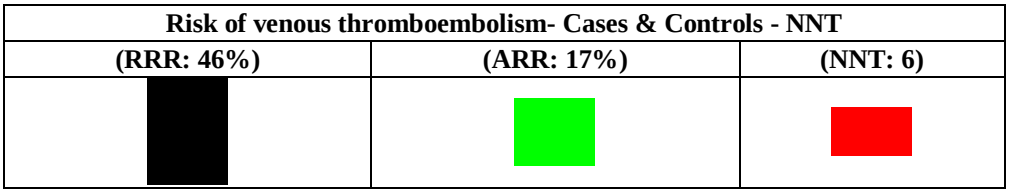

Fig. 1: Estimation of Number needed to treat (NNT) on risk of venous thromboembolism among cases and controls.

Significant association ($\chi 2$= 5.64) was obtained between risk of venous thromboembolism and diagnosis in controls, whereas no significant association was observed between risk of venous thromboembolism and their selected demographic profiles such as age, gender, BMI & diagnosis in cases (Table 4).

Table 4: Association between antipsychotics and risk of venous thromboembolism among nested cases and controls with their selected demographic profile.

S.No	Demographic profile	Cases	Controls
		χ^2- value, df, p-value	χ^2- value, df, p-value
1	Age	1.11, df=2, p=0.29	0.94, df=2, p=0.33
2	Gender	1.16, df=1, p=0.27	1.62, df=1, p=0.20
3	BMI	0.34, df=2, p=0.55	0.10, df=2, p=0.74
4	Diagnosis	0.63, df=2, p=0.42	**5.64, df=2, p=0.01**

DISCUSSION

Demographic profile according to the age group delineates that highest percentage (40%) were between 51-60 years among cases, whereas majorities 45% were between 51-60 years among controls. Gender depicts that paramount 60% & 57% were males among nested cases and controls respectively. These findings were consistently reported in a research work conducted by Mollard, L.M, (2018) stating that patients' median age was 66.0 years (IQR 49.0–76.0), 404 (54.9%) were men, and 61 (8.3%) were exposed to antipsychotics during follow-up.

According to BMI, highest percentages (50%) were obese in cases; however 47% had overweight in controls. Demographic profile according to the diagnosis revealed that majority 40% have been diagnosed with schizophrenia in cases, whereas 42% were diagnosed with BPAD in controls. Similar significant results were reported by Jiri Masopust, et.al., (2012) disclosing that potential etiopathogenetic factors leading to VTE during treatment with antipsychotic agents include sedation, obesity, elevation of antiphospholipid antibodies, increased platelet activation and aggregation, hyperhomocysteinemia, and hyperprolactinemia. Diagnoses of schizophrenia and/or bipolar affective disorder, as well as hospitalization or stress with sympathetic activation and elevation of catecholamine levels have been reported as known prothrombogenic factors.

The computed odds ratio between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls showed statistical significance with current timing of antipsychotic use, both typical & atypical antipsychotics, low and high potency of antipsychotics & oral mode of drug administration. Similar results were reported by Parker C, (2010) addressing that Individuals prescribed antipsychotic drugs in the previous 24 months had a 32% greater risk of venous thromboembolism than non-users, despite adjustment for potential risk factors (odds ratio 1.32, 95% confidence interval 1.23 to 1.42). Patients who had started a new drug in the previous three months had about twice the risk (1.97, 1.66 to 2.33). The risk was greater for individuals prescribed atypical rather than conventional drugs (adjusted odds ratio 1.73, 1.37 to 2.17, for atypical drugs; 1.28, 1.18 to 1.38, for conventional drugs). It also tended to be greater for patients prescribed low rather than high potency drugs (1.99, 1.52 to 2.62, for low potency; 1.28, 1.18 to 1.38, for high potency).

On the basis of the findings of the study, the following recommendations have been made for the further study. The present study can be conducted by enhancing the number of controls, besides propensity matching with cases. A randomized control trail can be conducted to determine the effect of treatment modalities and strategies for venous thromboembolism. Nursing theory can be developed, constructed and tested on antipsychotic drugs and risk of venous thromboembolism. Similar study can be replicated on large scale there by findings can be generalized for the target population.

CONCLUSION

Based on the findings of the study the following conclusions were drawn. The study findings revealed association between antipsychotic drugs and risk of venous thromboembolism among nested cases and controls, which showed statistical significance with current timing of antipsychotic use, both typical & atypical antipsychotics, low and high potency of antipsychotics & oral mode of drug administration.

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