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Research Article

A PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS THE QUALITY OF WARFARIN THERAPY AND VALIDATE THE IMPACT OF HAS BLED AND CHA2DS2-VASC SCORE IN THE PREVENTION OF STROKE IN INDIAN ATRIAL FIBRILLATION PATIENTS

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ABSTRACT

The aim of this study is to evaluate the quality of warfarin therapy and validate the impact of HAS-BLED and CHA2DS2-VSc score in thrombo prophylaxis for Indian atrial fibrillation patients. This was a prospective observational study which was conducted for a period of 6 months (February 2018- July 2018) at a tertiary care hospital of Trivandrum, Kerala and consisted of 92 patients. Time in therapeutic range (TTR) was assessed using Rosendaal method. Stroke risk and bleeding risk was assessed using CHA2DS2–VASc and HAS-BLED scores. The overall mean TTR value of 92 patients was 50.01 ± 29.38. The mean TTR values of good control group and poor control group were 74.58 ± 12.77 and 26.73 ± 20.09 (< 0.05 p value). Stroke risk and bleeding risk of the overall population was 3.09 ± 98.40 and 2.73 ± 1.62. The mean CHA2DS2–VASc and HAS-BLED score of the good control group was found to be 2.56 ± 68.54 and 1.36 ± 65.02 whereas for the poor control group, it was 3.58 ± 96.38 and 4 ± 1.16 (< 0.05 p value). Bleeding occurred only in the poor control group (10.9%) So, the overall quality of warfarin therapy in Indian atrial fibrillation patients was found to be suboptimal and the predictive ability of risk stratification scores was found to be useful.

Keywords: International normalized ratio, Time in therapeutic range, Warfarin, Atrial fibrillation

INTRODUCTION

Atrial fibrillation is a common type of arrhythmia, particularly seen in older individuals. It is estimated that its prevalence will be doubled in the next 50 years.[1] In the year 2050, Asia will have 72 million atrial fibrillation patients, and 2.9 million among them will suffer from AF-associated stroke.[2]

Previously, warfarin was the only choice of oral anticoagulant for treating atrial fibrillation patients who were at the risk of developing stroke. With the introduction of newer anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) in last few years, there is a wider spectrum of choice in drug therapy for preventing stroke in atrial fibrillation. According to the American college of cardiology, warfarin is recommended for anticoagulation in patients with atrial fibrillation who have mechanical heart valve. For patients who have non valvular atrial fibrillation, with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulation with warfarin or any of the newer anticoagulants are recommended.

The 4 major randomized control trials, namely, RE-LY, ROCKET, ARISTOTLE and ENGAGE, have already established the non-inferiority of novel oral anticoagulants (NOAC) against warfarin.[3-6] Studies on Asian population have also showed similar results.[7] However, studies of newer anticoagulants reported on an Indian population is limited; so warfarin still remains as the more reliable drug for Indian population. Yet warfarin still represents certain dilemmas, when it comes to treatment for non-valvular atrial fibrillation.

This research article mainly asses the advantages, predictiveness as well as dilemmas associated with oral warfarin therapy for non-valvular atrial fibrillation in Indian patients.

MATERIALS AND METHODS

Study design

Prospective observational study was conducted at the department of cardiology of a tertiary care teaching hospital in Trivandrum, Kerala. The study period was for 6 months (February 2018- July 2018) after getting clearance from Human Ethical Committee. Study population included patients who were diagnosed with non-valvular atrial fibrillation from the department of cardiology. Study was conducted on a population of 92 patients. Confidentiality of the collected data was sustained throughout the study period.

Sample size calculation

$$n = \left(\frac{Z_{\alpha/2}{}^2}{ME^2}\right)[\hat{p}(1-\hat{p})]$$

Where: Z = 1.96 is the 95% confidence value obtained from standard normal distribution. ME = 10% is the margin of error. $\hat{p}$ = 60% is the sample proportion of respondents who reported with more than sixty percent time in therapeutic range and having lesser side effects from previous study. In the present study,

Z = 1.96, ME = 0.1, P = 0.6

$$n = \frac{(1.96)^2 \times 0.6 \times 0.4}{(0.1)^2}$$

n = 92

Inclusion criteria

- Patients who were willing to participate in the study
- Patients diagnosed with non-valvular atrial fibrillation.
- Patients who have a CHA2DS2–VASc score of 1 or more.
- Patients who had been taking warfarin for a period of more than 6 months

Exclusion criteria

- Patients who were not willing to participate in the study
- Patients who had severe stroke within last 6 months.
- Patients who were newly prescribed warfarin.
- Patients with limited INR measurements.
- Patients who were prescribed aspirin or any newer oral anticoagulant

Study protocol

A written informed consent was taken from the patients as per ICMR biomedical guideline format. All information relevant to the study was collected from case records and direct interview with patient and/or caretaker. Study population consisted of 92 patients from the department of cardiology who were included according to the inclusion and exclusion criteria. Data collection form was designed to obtain demographic details, medical history, INR (international normalized ratio) values, co-morbidities, adverse drug reactions and number of current medications taken by each participant. CHA2DS2-VASc and HAS BLED scores were used for risk stratification of stroke and bleeding for each non valvular atrial fibrillation patient who were on warfarin therapy. In order to determine the quality of warfarin therapy, time in therapeutic range was calculated from the INR values obtained from each patient. The INR value of each patient was collected during each of their referral to the hospital where every patient had at least 3 INR measurements taken in total. The frequencies of INR monitoring and dose adjustments were based on the patients INR values. Each patient's time in therapeutic range (TTR) was calculated using the Rosendaal method. Patient who had a time in therapeutic range above 60%, were considered as good anti-coagulated patients and patients who had a time in therapeutic range below 60% were considered as poorly anti-coagulated patients.

Data analysis

The collected data of parameters from the study population were subjected to statistical treatment using appropriate statistical tools. Mean and standard deviation were calculated for continues study parameters while frequency and percentage were calculated for categorised study variables as descriptive statistics. Since collected data did not obey normality assumption, nonparametric statistical procedures were employed for statistically comparing groups based on various study parameters. Chi- square test was used for comparing good and poorly anti-coagulated groups for categorical variables if the expected frequencies were greater than 5, otherwise fisher's exact test has been applied. Man Whitney test was used for comparing good and poorly anti-coagulated groups for continuous study variables; P value lesser than 0.05 was considered as statistically significant.

Table 1: Mean age and Gender distribution

Group	Mean age	Males	Females
Good control	67.97	32 (72.7%)	12 (27.3%)
Poor control	71.29	24 (50%)	24 (50%)
Overall	69.70	56 (60.9%)	36 (39.1%)

Table 2: Mean number of co-morbidities and medications

Parameter	Group	N	Mean	SD	P
Number of Co morbidities	Good	44	2.90	67.57	0.000
	Poor	48	4.41	87.11	
	Overall	92	3.69	1.08	
Number of Medicines	Good	44	4.09	1.09	0.000
	Poor	48	8.58	1.39	
	Overall	92	6.43	2.58	

SD: Standard deviation

Table 3: Mean Time in therapeutic range

Parameter	Group	N	Mean	SD	P
Time in therapeutic range (TTR)	Good control	44	74.58	12.77	0.000
	Poor control	48	26.73	20.09	
	Overall	92	50.01	29.38	

Table 4: CHA2DS2–VASc score

Risk factors	CHA2DS2-VASc
Congestive heart failure	1
Hypertension: above 140 mmHg or treated with anti-hypertensive medication	1
Age ≥75 years	2
Diabetes mellitus	1
Prior Stroke or Transient ischaemic attack or Thromboembolism	2
Age 65–74 y	1
Age 50–74 y	-
Sex category (female sex)	1
Maximum score	9

Table 5: HAS BLED score

Risk factor	HAS-BLED
Hypertension (systolic blood pressure > 160 mm Hg)	1
Abnormal renal and liver function* (1 point each)	1 or 2
Stroke	1
Bleeding tendency/predisposition	1
Labile INRs (if on warfarin)	1
Elderly (e.g. age > 65 y)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

Table 6: Stroke and Bleeding risk assessment

Parameter	Group	N	Mean	SD	P
CHA2DS2–VASc	Good control	44	2.56	68.54	0.000
	Poor control	48	3.58	96.38	
	Overall	92	3.09	98.40	
HAS BLED	Good control	44	1.36	65.02	0.000
	Poor control	48	4.0	01.16	
	Overall	92	2.73	01.62	

Table 7: Proportion of stroke

Group	Stroke		CHI Square	P value
	Yes	No		
Good control	0	44	12.650	0.000
Poor control	12	36		
Overall	12	80		

Table 8: Proportion of bleeding

Group	Bleeding		CHI Square	P Value
	Yes	No		
Good control	00	44	10.285	0.001
Poor control	10	38		
Overall	10	82		

RESULTS AND DISCUSSION

Vitamin k antagonists have been shown to be effective in the treatment and prevention of thromboembolic events; however they possess many numbers of drawbacks like constant need of monitoring, fluctuating values of INR values, risk of thromboembolic events and risk of bleeding. Due to such drawbacks, it is difficult to predict the effects of warfarin treatment. So, our study mainly tries to explore this incalculable nature of warfarin therapy by analysing current conundrums as well as its advantages in treatment associated with Indian atrial fibrillation patients.

In this study, we analysed the data of 92 atrial fibrillation patients. 92 patient population were divided into good control anti-coagulation group and poor control anti-coagulation group based on the TTR values (time in therapeutic range) calculated from the collected INR values of patients. Thus based on this, we were able to assess the impact of different clinical parameters on the overall population as well as the good and poorly anti coagulated group.

Table 1 shows the mean age and gender distribution of the overall population as well as good control group and poor control group within the population. The mean age of overall population was found to be 69.70 ± 7.95. The mean age of the good control group was found to be 67.97 ± 5.47 whereas the mean age of the poor control group was found to be 71.29 ± 9.47. Total proportion of males was 56 (60.9%) and females were 36 (39.1%). Proportion of males in the good control group was 32 (72.7%) and that of females were 12 (27.3%). Proportion of males and females were similar in the poor control group; each 24 (50%).

In terms of gender and age, we did not find any significant difference between any of the groups. However, the numerical number of female population was found to be higher in the poor anti-coagulated group when compared to the good control group and the mean age of poorly anti-coagulated group was higher than the rest.

Table 2 shows the proportion of co-morbidities and medicines used by each group. Mean number of co-morbidities found in the overall population was 3.69 ± 1.08, with good control group having 2.90 ± 67.57 and poor control group having 4.41 ± 87.11. Significant differences were found between good control and poor control group (P value < 0.05). The mean number of medicines used by the whole study population was found to be 6.43 ± 2.58. The mean number of medicines used by the good control group and poor control group was found to be 4.09 ± 1.09 and 8.58 ± 1.39. So, there was statistically significant difference between them (P value < 0.05). Both of them are major risk factors for stroke and cardiovascular diseases. Total number of medications and co-morbidities were found to be statistically significant contributing factors influencing the quality of warfarin therapy.

The stratification of patients according to TTR values were conducted as follows: TTR value of > 60% was considered to be good controlled anti-coagulation and a TTR value of < 60% was considered as poorly controlled anti-coagulation. The mean TTR value of 92 patients was found to be 50.01 ± 29.38. Good control group contained 44 patients (47.82%) and poor control group contained 48 patients (52.17%). The mean TTR value of good control group was 74.58 ± 12.77 whereas the mean TTR value of poor control group was 26.73 ± 20.09. There was significant

difference between the groups (< 0.05 p value). Table 3 shows the mean TTR values obtained.

The efficacy and safety of oral vitamin K antagonists such as warfarin depend strongly on the percentage of TTR, with the maximum benefits being evident when the TTR is > 70%. It is well-known that poor control of anti-coagulation increases the risks of thrombotic and haemorrhagic events. The consistency of an effective INR is reflected by the TTR, which is a measure of the period in which the patient was in an optimal INR range. Time in therapeutic range (TTR) can be said as an indicator that shows the quality of warfarin therapy. The time in therapeutic range is calculated based on the patient's INR values. While on warfarin therapy, the INR of the patient has to be constantly monitored and maintained within the normal range (2.0 – 3.0). The TTR and INR values are correlated with the incidence of adverse events due to warfarin.[8] So maintaining the TTR and INR values within the normal range can prevent any adverse events and improve the warfarin therapy. Time in therapeutic range shows the amount of time the INR was in normal range. Those patients who achieve more than 70% TTR receive maximum benefit from warfarin therapy. Patients are at a lower risk of any thromboembolic or bleeding event when their TTR values are over 70%. But the value of TTR reported in studies are varying, suggesting the difficulty in maintaining the TTR above 70%. Bahram-Fariborz Farsad *et al* study reported a mean TTR of 54.9% and took 50-70% TTR values as the intermediate level of anti-coagulation in their Iranian study population.[9] But Daniel Caldeira *et al* reported 44.3% of their patients who had a mean TTR < 60%, were at an increased risk of thrombotic and hemorrhagic events.[10] Even the larger randomized trials of newer oral anticoagulants and warfarin in Atrial fibrillation, provided further data about world-wide difficulty in maintaining the TTR level. The mean TTR values of the major large randomized trials (ROCKET-AF trial, ARISTOTLE trial and the RELY trial) were 55.2%, 62.2% and 64%.[3-5] So there are no standard of accepted range for TTR. The general consensus that we can deduct from these studies is the correlation between increase in TTR values and improvement of the patient outcomes on warfarin therapy. So this is the reason why we took above 60% and below 60% as good and poor control group. In our study, the overall quality of warfarin therapy was found to have a mean TTR value of 50.01 ± 29.38. Our findings are consistent with the studies of Bahram-Fariborz Farsad *et al*, Zubaid *et al* and RE-LY trial. In the Zubaid *et al* study, they evaluated the quality of warfarin therapy for 369 patients with non-valvular atrial fibrillation and estimated TTRs by the Rosendaal method.[11] They reported a mean TTR of 52.6% in their sample, which is close to the mean TTR determined in the present study (50.01 ± 29.38).

CHA2DS2–VASc score and HAS BLED were the major scores used for the stroke and bleeding risk assessment of each group. In our study, The CHA2DS2–VASc score of the good control group was found to be 2.56 ± 68.54 and that of the poor control group was found to be 3.58 ± 96.38. The overall risk of stroke was found to be 3.09 ± 98.40. Table 4 shows the award of score in CHA2DS2–VASc scale.

The Mean bleeding risk or the mean HAS BLED score of the good control was found to be 1.36 ± 65.02 while that of the poor control group was found to be 4.0 ± 1.16. The overall risk of bleeding was found to be 2.73 ± 1.62. So, in our study there were significant differences in stroke and bleeding risk for each group (< 0.05 p value). Table 5 shows the award of score in HAS BLED scale.

Stroke risk and bleeding risk are the 2 major risk factors that have to be taken into consideration before treating a patient with oral anti-coagulants. According to the guidelines recommended by American college of cardiology, for patients with a CHA2DS2-VASc score (stroke risk score) of 0, it is reasonable to omit antithrombotic therapy and for patients with CHA2DS2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered whereas for patients with non-valvular atrial fibrillation, with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. In the case of bleeding, no standard bleeding risk score is recommended, but HAS BLED is the bleeding risk score that has been associated with maximum predictive ability.[12] Both of these scales have not been validated in an Indian population.[13] So, we are the first study to report the utility of these scores in Indian patients with limited sample size. Table 6 shows the mean stroke and bleeding risk of each group.

Since there was significant difference in both stroke risk as well as bleeding risk between the groups, this establishes the fact that the poorly anti-coagulated group were at a higher risk than the good control group.

The efficacy endpoint was taken as stroke (ischaemic/ hemorrhagic) and bleeding end point was defined as any type of bleeding-fatal or symptomatic bleeding in a critical area or organ, such as intracranial, gum, gastrointestinal or nasal bleeding. Stroke and bleeding were taken as the associated outcomes to determine the predictive ability of CHA2DS2–VASc and HAS BLED score.

The proportion of stroke patients were found to be 12 (13%) in poorly anti coagulated group while none of the patients among the good control group suffered stroke. Ischaemic stroke occurred in 8 patients (8.7%) while hemorrhagic stroke occurred in 4 patients (4.3%). Table 7 shows the proportion of stroke.

The proportion of bleeding patients were found to be 10 (10.9%) in the poorly anti-coagulated group while none of the patients in the good control group had bleeding. 4 types of bleeding occurred, namely, ICH (Intracranial haemorrhage) in 1 patient (1.1%), nasal bleeding in 2 patients (2.2%), Gastro intestinal bleeding in 3 (3.3%), and haematuria in 4 (4.4%). There was significant difference in the proportion of stroke and bleeding between each group (< 0.005 p value). Table 8 shows the proportion of bleeding.

The proportion of stroke and bleeding were higher in the poorly anti-coagulated group (13% and 10.9%). This indicates the better predictive ability of CHA2DS2–VASc and HAS BLED score in Indian population, when it comes to bleeding and stroke as poorly anti-coagulated had higher stroke and bleeding risk scores.

CONCLUSION

There are no reports in current literature regarding the assessment of quality, risk stratification and its associated outcomes in Indian atrial fibrillation patients who are on warfarin therapy. The quality of warfarin therapy was found to be not satisfactory as it was only effective for patients with a lesser stroke and bleeding risk. CHA2DS2–VASc and HAS BLED scores were found to be useful in predicting the adverse events in this particular study. Number of medications and number of co-morbidities were the only factors which were found to be the contributing factors to poor anti-coagulation. Further studies needs to be conducted on a larger population in order to solidify our observation. Furthermore, for Indian patients with a higher stroke and bleeding risk, newer oral anti-coagulants might be effective for non-valvular atrial fibrillation as it has shown promising results

outside India. This is another area of research which has to be explored in future.

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