INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 5; Issue 07(A); July 2019; Page No. 4355-4358
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr201907695

Research Article

ANTICOAGULANT ASSOCIATED STROKE, AN OBSERVATIONAL RETROSPECTIVE STUDY IN TERTIARY CARE HOSPITAL IN NORTH INDIA

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ARTICLE INFO

Article History:
Received 13th April, 2019
Received in revised form 11th May, 2019
Accepted 8th June, 2019
Published online 28th July, 2019

Key words:
Stroke, oral anticoagulants, thromboembolic disorders, warfarin, hemorrhagic stroke

ABSTRACT

Introduction: Anticoagulant treatment is indicated for the treatment and prevention of recurrent thromboembolic disorders. Vitamin K antagonists are widely used oral anticoagulants worldwide. Vitamin K antagonists act by inhibition of vitamin K epoxide reductase and are often used for long-term anticoagulation. The benefits of oral anticoagulants have been clearly established in well-designed clinical trials. Coumarin preparations are commonly used vitamin K antagonists in clinical practice. Warfarin is the most widely used oral anticoagulant (OAC) in the world, although acenocoumarol, phenprocoumon or anisindione are also frequently prescribed in several countries. Nonetheless, OAC are also notorious for having a narrow therapeutic index, numerous drug and dietary interactions, and a significant risk of serious bleeding that includes hemorrhagic stroke.

Material and methods: This study was an observational retrospective study conducted at the Government medical college and SMHS over a period of 1yr.A detailed initial assessment of the patients was done, clinical indication for the use of anticoagulants and the duration of treatment was noted. An NCCT of the Brain was performed on admission to note the site and volume of bleed and intraventricular extension. Patients were followed for 30days with clinical, biochemical parameters and the outcome was noted. All statistical analysis was performed using SPSS version 21 for Windows (IBM). A P value < 0.05 was taken to be statistically significant.

Result: A total of 422 stroke patients were studied, out of which 224(53.08%) had ischemic and 198(46.91%) had hemorrhagic stroke. The age distribution shows mean age of patients with OAC-ICH was 61yrs. 56.25% of our patients were females and 43.75% were males. The mean duration of use of anticoagulants in our cohort was 2.2 yrs. out of 16, 6 patients were on acitrom, 9 on warfarin and 1 on dabigatran. All our patients had deranged coagulation parameters on admission with PT/INR >8. Sixteen patients (ie 0.04% of all strokes and 8.08% of all ICH) were associated with oral anticoagulant use (OAC-ICH).

Conclusion: oral anticoagulant associated ICH is a significant complication of these drugs and with the increasing use of these drugs in thromboembolic disorders, its incidence is only expected to rise.

INTRODUCTION

Anticoagulant treatment is indicated for the treatment and prevention of recurrent thromboembolic disorders.[1] Vitamin K antagonists are widely used oral anticoagulants worldwide.[2,3] Vitamin K antagonists act by inhibition of vitamin K epoxide reductase and are often used for long-term anticoagulation.[3] The benefits of oral anticoagulants have been clearly established in well-designed clinical trials.Coumarin preparations are commonly used vitamin K antagonists in clinical practice.[4]Warfarin is the most widely used oral anticoagulant (OAC) in the world, although acenocoumarol, phenprocoumon or anisindione are also frequently prescribed in several countries. Warfarin inhibits the vitamin K-dependent posttranslational carboxylation of glutamate residues on the N-terminal regions of coagulation factors II, VII, IX and X by inhibiting the conversion of vitamin K 2, 3-epoxide to reduced vitamin K [5].The benefits of OAC for thromboembolic protection are supported by a high level of evidence in patients with several cardiac conditions, atrial fibrillation or a history of venous thromboembolism [6]. Nonetheless, OAC are also notorious for having a narrow therapeutic index, numerous drug and dietary interactions, and a significant risk of serious bleeding that includes hemorrhagic stroke [7]. In order to maximise protection against thromboembolic complications while minimising the risk of bleeding associated with VKA therapy, the intensity of OAC should be maintained within a narrow therapeutic range(TTR). Apart from non-bileaflet mechanical heart valves and mechanical heart valves in the mitral position, where a higher intensity of OAC therapy is required, an international normalised ratio (INR) of 2.0-3.0 has long been identified as the optimal TTR for most clinical conditions at risk for thromboembolic events[8]. Other limitations include delayed onset of action necessitating a bridging therapy with heparin initially, genetic heterogeneity in pharmacokinetic response and food as well as drug interactions.[9]Nonetheless, bleeding represents the major complication of OAC therapy, even when OAC is properly prescribed[10].

The expected incidence of bleeding during long-term VKA therapy is about 10%-17% per year for all events, 2%-5% per year for major bleeding, and 0.5%-1% peryear for fatal bleeding[11]. The reported occurrence of intracranial

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haemorrhage (ICH), which represents the mostly feared bleeding complication of VKA therapy because of its high disability and/or fatality rate, is in the range of 0.2%-0.4% per year[10,12].

In a retrospective Indian study, overall anticoagulant control was generally poor with many patients in a state of under anticoagulation for most period of anticoagulant treatment (Out of a total of 1631 PT ratios and INRs recorded, only 17.8% were in the therapeutic range).[12] Another Indian study showed that the knowledge base of clinicians regarding OAC management was unsatisfactory with a tendency to under-dose patients due to fear of bleeding.[13] Indians with their different dietary habits are more prone for warfarin food interactions. Green leafy vegetables, cabbage, cauliflower, and other foods rich with vitamin K in the Indian diet cause lability in INR values. Over the counter medications such as non-steroidal anti-inflammatory drugs, herbal foods (e.g. garlic, fenugreek) and use of concomitant antituberculous drugs (isoniazid or rifampicin) may also alter INR values and result in under or over anticoagulation.[14] NOACs with their predictable pharmacokinetics and anticoagulant effects preclude the need for routine laboratory monitoring. Compared with warfarin, they have lower risk of intracranial bleeding, fewer food and drug interactions.[15,16]

Aims and objectives

In our study we aim to observe the incidence of anticoagulant induced intra cranial haemorrhages and to elucidate the type oral anticoagulant commonly associated with the bleeding diathesis.

MATERIAL AND METHODS

This study was an observational retrospective study conducted at the Government medical college and SMHS over a period of 1yr. Ethical approval was obtained from the Research Ethics Committee and consent was obtained from all participants. Patients were excluded if valid consent could not be obtained.

A detailed initial assessment of the patients was done, clinical indication for the use of anticoagulants and the duration of treatment was noted.GCS at the time of admission noted along with the volume of bleed, the location of bleed and the need for surgical intervention.ICH score was calculated at admission. Relevant clinical past and present history including the concomitant use of anti-platelets was noted.

Routine biochemical investigations were performed. PT/INR and a PTT was done in each of the patients to determine their coagulation status.

An NCCT of the Brain was performed on admission to note the site and volume of bleed and intraventricular extension.

Patients were followed for 30days with clinical, biochemical parameters and the outcome was noted.

All statistical analysis was performed using SPSS version 21 for Windows (IBM). Continuous data were assessed for normality visually by plotting histograms. For normally distributed data the mean (standard deviation) and parametric tests were used and for nonnormally distributed data the median (interquartile range (IQR)) and non-parametric tests were used. Categorical data, quoted as n(%), were assessed using cross-tabulation and the chi squared test for independence. A P value < 0.05 was taken to be statistically significant.

RESULTS

A total of 422 stroke patients were studied, out of which 224(53.08%) had ischemic and 198(46.91%) had hemorrhagic stroke. The age distribution is shown in table 1 with mean age of patients with OAC-ICH was 61yrs. 56.25% of our patients were females and 43.75% were males

Table 1 Age distribution

Age distribution(yrs)	% of patients
40-50	12.5%
50-60	25%
60-70	56.25%
70-80	6.25%

The clinical indications for use of anticoagulants is listed in table 2.

Table 2 indication of anti coagulation

Clinical indication	%age of patients
DVT	12.5%
AF /cardioembolic stroke	18.75%
DCM / AF	25%
HTNCVD / AF	37.5%
Post MVR	6.25%

The mean duration of use of anticoagulants in our cohort was 2.2yrs.out of 16, 6 patients were on acitrom, 9 on warfarin and 1 on dabigatran.

The spectrum of clinical presentation is shown in table 3.

Table 3 clinical presentation of patients

Clinical presentation	%age of patients
Hemiparesis	43.75%
Altered mental status	31.25%
Headache	12.5%
Recurrent vomitting	6.25%
Aphasia	6.25%

The distribution of ICH score is shown in table 4.with volume of bleed less than 30ml in 50% of patients.

Table 4 ICH score in patients

ICH score	No. of patients
0	5
1	2
2	4
3	3
≥4	1

All our patients had deranged coagulation parameters on admission with PT/INR >8. NCCT brain revealed that 14 patients had intracerebral haemorrhage, 1 patient had SAH and 1 had SDH. The patients were followed for 30days, around 50% patients improved, 25% patients developed complications (aspiration) and worsened while 25% patients expired.

DISCUSSION

OAC therapy with VKAs is the most effective available treatment for prevention of thromboembolic complications in frequent clinical conditions, such as atrial fibrillation, venous thromboembolism, prosthetic heart valves, and cardiogenic stroke. Such efficacy comes at the price of an increased risk of overall, major and ICH bleeding. Until recently, vitamin K antagonists such as warfarin, nicoumalone (acitrom) were the mostly widely used agents. However, these OAC are also notorious for having a narrow therapeutic index, numerous drug and dietary interactions, and a significant risk of serious bleeding that includes hemorrhagic stroke [7] Newer anticoagulant agents like dabigatran, rivaroxaban have been introduced as these have less drug-drug and drug food interactions, lesser need to monitor the therapeutic effects and lesser side effects[17].Nonetheless, bleeding is a major side effect of anticoagulant agents.

We studied 422 stroke patients over a period of 1yr, the mean age of patients enrolled in our study was 61yrs and 62.5% of patients were aged more than 60yrs.out of which 224(53.08%) had ischemic stroke while 198(46.91%) had an intracranial bleed.43.75% patients presented with hemiparesis, 331.25 % with altered mental state with a mean GCS of 9,12.5% with headache, 6.25% with recurrent vomiting and 6,25% with aphasia.6(37.5%) patients were taking acitrom, 9(56.25%) patients were on warfarin and 1(6.25%) on dabigatran and the mean duration for which our patients were on OACs was 2.2yrs.In around 50% patients the volume of bleed was less than 30ml. ICH score was calculated at the time of admission to prognosticate the patients and 11(68.75%) patients had ICH score <3 and 4(25%) had >3.16 patients (ie 0.04% of all strokes and 8.08% of all ICH) were associated with oral anticoagulant use(OAC-ICH). None of our patients were on concomitant anti-platelets. The clinical indications for which our patients were prescribed OACs were: DVT, AF with cardioembolic stroke, Dilated cardiomyopathy with AF, Hypertensive heart disease with AF, Valvular AF, Post MVR. similar results were found by Haart *et al* who reported About5-12% of ICH is related to OAC, leading to an estimatedannual incidence in the USA of nearly 3,000.[18,19,20]. In our study the incidence of OAC-ICH with varied clinical condition was atrial fibrillation we found around in 10 (62.5%) out 16 patients and 4(25%) patients of mv replacements and 2 (12.5%)patient of DVT as was seen, In randomised trials, the risk of major bleeding associated with vitamin K antagonists varied according to the clinical condition that motivated the treatment, mechanical heart valves (1-8.3%), atrial fibrillation (0-6.6%), coronary heart disease (0-19.3%), venous thromboembolism (0-16.7%),or ischemic cerebrovascular disease (2-13%) [21] All our patients had deranged coagulation parameters, with INR>8 in all patients. An NCCT brain was done which revealed that 14 patients had intracerebral haemorrhage, 1 patient had subdural haemorrhage and one SAH. We went a step further and divided patients having ICH into two groups one who were on OACs and other having ICH due to any other cause and tried to review the location of bleed which is usually found in OAC-ICH and we found that basal ganglia bleed was commonest site occurring in 30% of patients of OAC-ICH where as 23% patients had cerebella bleed with patients in other group showed 24% having basal ganglia bleed and 20% showed thalamic bleed and only 14% showed cerebellar bleed. All these patients were followed over a period of 30 days, around 50% patients improved, 25% patients developed complications (aspiration pneumonitis) and prolonged morbidity while 25% patients expired while as in control group 58.8% patients improved and where discharged home, 21% Patients developed complications 18% patients died in hospital, Flaherty *et al* and Flouke *et al* have reported ICH is the most threatening stroke subtype, particularly in men, with a mortality rate between 30 and 55% Aggregated data shows thatthe outcome of patients with OAC-ICH is worse than in patients with spontaneous ICH, and that increased mortality obeys as much to a higher incidence of larger haemorrhages, as to the older age and severe comorbidity frequently observed in patients with OAC-ICH [22,23,24].

In Indian scenario many factors leads to development of oral anticoagulant associated bleed, modifiable factors being education about the drug food interaction and drug,-drug integration being one of them, therapeutic drug dose monitoring is also one of the factors and also the non-compliance to the medication and over the counter drug distribution. Kakkar N *et al* [25] in their study have shown that outpatient anticoagulant control was generally poor with inadequate pretherapeutic assessment an unacceptably high proportion of subtherapeutic PT/INR values and high complication rates[25]. Praveen SV *et al* [26] reported that PT monitoring was irregular in 25% of patients. They also found that in patients on mechanical heart valves on VKAs the morbidity increased over years of follow-up and inadequate anticoagulation is associated with increased risk of stroke. Among non modifiable factors genetic variation and multivariate single nucleotide polymorphism has effect on drug distribution absorption and elimination, Although most of the patients in Indian subcontinent are found to use warfarin as anticoagulant of choice due to cost effectiveness this is the reason the incidence of OAC associated bleed was more in warfarin group but if we compare the incidence of bleed in warfarin and acitrom with the equal percentage of patients we will get a different result this was out of scope of this research as our study mostly contained patients on warfarin.

Further we need to work on the genetic polymorphism and association of oral anticoagulant associated bleed in Indian population and a comparative study between different oral anticoagulants to know the therapeutic window and prevalence of ICH in patients taking different newer OACs and outcome in these patients.

Lastly we conclude with statement that OAC-ICH is a well recognised entity which needs close monitoring in patients on oral anticoagulants and close follow up and coagulation profile measurement, although we cannot predict the occurrence of bleed but we can keep the patient in close therapeutic range of the coagulation profile and early diagnosis and treatment can be made possible by close follow up.

CONCLUSION

1. oralanticoagulant associated ICH is a significant complication of these drugs and with the increasing use

of these drugs in thromboembolic disorders ,its incidence is only expected to rise.
2. Oral anticoagulant associated ICH has worse prognosis and outcome as compared to ICH due to some other comorbidities.
3. We need to work on patient education about drug interactions and therapeutic coagulation profile monitoring and close follow up of patients who are on oral anticoagulants.

Gene study and polymorphism and multivariate association of drug interaction in Indian population and comparative analysis of sub groups of oral anticoagulants should be initiated and funded at a larger scale both in urban and rural population.

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