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Comparison of Point of Care Device with Lab Monitoring of INR Assay for Monitoring of Anticoagulant Therapy

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Abstract: ***Objective: To test whether point of care measurement is as safe, as lab measurement of patient as assessed by therapeutic international normalized ratio(INR) control. Methods:It is a hospital based prospective comparative study, including 80 patients, dividing into group 1, in which INR was measured with the help of point of care device at OPD and in group 2, in which INR was measured by standard lab and accordingly dose adjustments were done monthly and were followed up for 6 months. Results: The incidence of major bleed was 5% in group 2 and no major bleeding events in group 1. The incidence of thromboembolic events was equal in both groups which was 5% in each group. The incidence of major events was 5% and 10% patient year respectively in group 1 and 2. The incidence of minor bleeding events was 20% and 10% respectively in group 1 and 2.Overall incidence of adverse event was 25% and 20% respectively in group 1 and 2. Percentage of time in therapeutic range which can be considered as surrogate marker for clinical effectiveness of INR control for propensity of adverse event is significantly more in group 1(59.59%) than group 2(48.95%). Conclusion: INR measurement with point of care device for monitoring of oral anticoagulant therapy is as safe, as lab measurement by therapeutic international normalized ratio(INR) control.***

Keywords: Point of care(POC), International normalized ratio(INR)

1. Introduction

Oral anticoagulation therapy with vitamin K antagonist(VKA) has been shown reduce thromboembolic events in multiple clinical contexts. [1, 2] These include atrial fibrillation, treatment of deep-vein thrombosis, prosthetic heart valves, and acute myocardial infarction. Oral anticoagulation(OAC) with warfarin or other Vitamin K Antagonist(VKA) like Acenocumarole or Phenprocoumon could potentially prevent more than half of the strokes related to atrial fibrillation and heart valve replacements with a relatively low risk of major bleeding complications. [3] However, much of this potential is still not obtained because of under and suboptimal use. [4] The number of patients receiving OAC drugs has been constantly increasing during the last decade. Reasons include improvements in clinical outcomes, increasing common disease indications for their use, and improvements in anticoagulant safety. [5, 6, 7]

Due to the complex pharmacokinetics of warfarin, continuous monitoring and dose adjustments are required. [8] VKA treatment requires regular monitoring of prothrombin time (PT) with dose-adjustment by a specialized hospital service, primary care physician, registered nurse, nurse practitioner, or pharmacist [9, 10].

Current models of oral anticoagulation management include the traditional hospital outpatient model which include laboratory testing of International Normalized Ratio (INR) coupled with VKA dosage adjustment by a physician or through an anticoagulation clinic and various forms of community-based models, all requiring patient attendance at a clinic. [11]

The introduction of portable monitors(point-of-care devices) allows the patient to self-test at home or clinic with a drop of whole blood. Self-management of VKA by the patient is an evolving model whereby trained patients can test their INR using point of care (POC) systems and adjust their OAC dosages. [12]

POC coagulation testing has been termed the most rapidly growing point of care application in the hospital setting. This rapid growth implies a widespread acceptance of the use of point of care coagulation assays, yet it is unclear whether documentation exists showing a clinical advantage to these methodologies. [13]

2. Material and Methods

Aim

To test whether POC measurement is as safe, in terms of clinical effectiveness, as lab measurement of patient as assessed by therapeutic INR control in patients on oral anticoagulation.

Source of Data

The patients attending cardiology clinic and medical department of a tertiary care hospital who were on oral anticoagulant therapy (OAT) for various indications were included in this study.

Study Design

Prospective comparative study.

Inclusion Criteria
All patients, adults(age 18 years or more) on long-term anticoagulant therapy(treatment duration longer than two months) irrespective of the indication for treatment.

Exclusion Criteria
Age less than 18 years, concomitant chronic liver disease, uncontrolled hypertension(BP > 180/110 mmHg), uncontrolled diabetes(HbA1c > 7%), previous cerebrovascular events (CVE) and unwilling to participate in study.

Methods

A written informed consent was taken for all the patients. Patients' demographics, medical history including various comorbidities, concomitant drug use, current smoking status and physical examination were recorded as baseline. Vital signs, physical examination and adverse events were assessed during each follow up visit.Initially 45 patients were identified and selected in group 1 who were being managed with POC device for INR out of which 4 met exclusion criteria and 1 did not turned up for study. 47 patients were selected from lab monitoring group out of which 5 were excluded as they fell into exclusion criteria and 2 did not wanted to participate into study. Overall 40 patients were followed up in each group. There was no loss to follow up. In patients of group 1 INR was measured with the help of POC deviceat Out Patient Department(OPD)and OAT dose adjustment were done by experienced physician or cardiologist. In patients of group 2 INR was measured by standard lab and accordingly dose adjustment were done as in group 1. In both the group monthly INR measurement and dose adjustment of OAT was done for 6 months. However, if any change in dose was required then repeat INR testing was done after 15 days and if OAT needed to be withheld due to high INR or any adverse events in that case repeat INR was done after 3 days. Number of adverse events were recorded in form of major bleed(overt gastrointestinal bleed, alveolar hemorrhage, intracranial bleed requiring hospitalization), minor bleed(petechae, purpura or ecchymosis, subconjuctival hemorrhage not requiring hospitalization) or thromboembolic events(CVE, mesenteric ischemia, central retinal artery occlusion) or any mortality directly attributed to OAT induced adverse event.

Point of care device for INR measurement: Coaguchek XS by Roche. It uses human recombinant thromboplastin as reagent and works on the principle of electrochemical detection of thrombin activity. It uses capillary blood sample for test. During each visit capillary blood sample was taken by lanceting the finger and test was done at point of care as recommended by the manufacturing company. Based on test result, dosage adjustment of OAT was done and records were maintained for each follow up visit.

The standard laboratory used rabbit brain thromboplastin as reagent and works on the principle of electrochemical detection. A venous sample of 2.7 ml were taken in citrate vacutainer under universal precautions and sent to laboratory within 2 hours for measurement. Based on the test results the oral anticoagulant dose was adjusted and records were maintained.

Data was analysed using following statistical tests - Pearson Chi-Square test, Fisher's exact test and unpaired T test.

3. Results and Observations

There were 40 patients in each group and total number of patients followed up in study was 80.Group 1 and group 2 consisted of patients whose INR was measured with POC device and conventional lab monitoring respectively. The various characteristics of study population and indication for OAT has been mentioned in table 1.

In present study major events were taken as major bleeding or any thromboembolic event. There was 1 major bleeding event in form of gastrointestinal bleed in group 2 while nil in group 1. Among thromboembolic complications in POC group one patient had mesentry artery embolism while one patient in conventional group had embolic CVE. The number of minor events in this study in group 1 was 4 and in group 2 was 2.The incidence of bleeding events in both the groups(major + minor bleeds) was 20% patient yearin POC group and 15% patient year in conventional group. The overall incidence rate of adverse events(major + minor) is 25% in group managed with POC device and 20% patient year in conventional lab monitoring group. The percentage of time within targetrange was 59.59% in group 1 and 48.95% in group 2 in the present study.

Table 1: Demographic profile of patients of the two groups

Variables	Group 1	Group 2
Number of patients	40	40
Gender		
Males	17	20
Females	23	20
Mean age (in years)	47.53	50.78
Indication for oral anticoagulant therapy		
• Atrial fibrillation	17	19
• Aortic valve replacement	1	5
• Atrial clot	1	0
• Coronary artery disease	6	2
• Cortical venous thrombosis	0	3
• Deep vein thrombosis	3	2
• Aortic + Mitral valve replacement	3	1
• Mitral valve replacement	7	7
• Pulmonary thromboembolism	2	1
Risk factors		
• Diabetes mellitus	3	6
• Hypertension	6	6
• Smoking	6	10
• Significant drug interaction	4	3

4. Discussion

Till date various studies have been done which compared therapeutic INR measurement and OAT dosage adjustment by routine care (lab monitoring and review with physician) and by self-using a portable coagulometer. But no such Indian study has been done till date to best of our knowledge which has compared the clinical effectiveness of portable coagulometers with lab monitoring taking INR as control. Beside this portable Coagulometer are still costly and requires some amount of technical skill and dexterity to perform self-testing and person also needs education to do dosage adjustment by self which can be a hurdle in Indian

scenario as a significant proportion of Indian population belongs to low socioeconomic class and is uneducated.

However, if portable coagulometers are used at clinics in outpatient departments, it can cut down the lengthy time consuming visits along with initial cost, and provide other advantages over conventional lab monitoring as explained previously, if proven equally or more effective.

This study titled "To test whether POC measurement is as safe, in terms of clinical effectiveness, as lab measurement of patient as assessed by INR control" was carried out at a tertiary health care hospital.

The patients taken in our study were comparatively younger than most of the other similar studies. The mean age of patients in study of Sawicki et al. was 55 years, [14] in Fitzmaurice et al 2005 and Menendez et al it was 65 years. [15, 16] This difference can be explained by the fact that our study has been done at a tertiary care service hospital where most of the patients are of young age group. Besides thatmajor burden of patients had rheumatic heart disease leading to atrial fibrillation or requiring heart valve replacement which affects young individuals. [17, 18] However, in western countries where most of the studies has been done the major cause for heart valve replacement is atherosclerotic valve disease which occurs in older individuals and atrial fibrillation is also associated with old age. [19]

In our study there were more females 53.8% as compared to males 46.3% although not statically significant. Study done by Beyth RJ et al also consisted of more female patients 56% than male patients 44%. However, in other studies done by Fitzmaurice et al in 2005 had 35% female population and Menendez et al in 2005 had 46.9% females and 53.1% males.**Error! Bookmark not defined.**' **Error! Bookmark not defined.**' [20]

The most common indication for OAT was Atrial fibrillation involving 45% patients followed by heart valve replacement involving 30% patients (aortic valve - 7.5%; mitral valve - 17.5%; double valve replacement - 5%), coronary artery disease 10%, Deep Venous Thrombosis(DVT)and pulmonary embolism(PE) together constituted 7.6% patients and others (atrial clot and venous stroke) constituted 4.1% of total study population. Almost similar indications were there in study done by Fitzmaurice et al. in 2005 whose indications in decreasing order were atrial fibrillation > prosthetic valve > DVT/PE > cardiomyopathy > Transient Ischemic Attack/stroke; Menendez et al. Atrial fibrillation > aortic valve replacement > mitral valve replacement/double valve replacement > venous thromboembolism; and Ryan et al. prosthetic valve > atrial fibrillation > DVT/PE > others.**Error! Bookmark not defined.**' **Error! Bookmark not defined.**' [21] So the 2 most common indications for OATs are atrial fibrillation and prosthetic valve closely followed by coronary artery disease and venous cause of thromboembolism.

The various associated risk factors for adverse events in our study which were identified are as follows: Diabetes mellitus - 7.5% in POC group and 15% in conventional group. Hypertensives were equal in both groups15%. Significant drug interaction was identified in 10% patients in group 1 and 7.5% in group 2 all with amiodarone. In study done by Menedez et al. almost 45% patients were hypertensives and 14.5% patients were diabetic and in study of Fitzmaurice et al. 2005 45% patients were hypertensives.**Error! Bookmark not defined.**' **Error! Bookmark not defined.** This difference is because of uncontrolled diabetes and hypertension were taken as exclusion criteria in our study. Besides that, the mean age of patient in our study is quite less as compared to these studies as increasing age is associated with diabetes and hypertension.

The incidence of clinical complications or adverse events is of major interest while studying the clinical effectiveness of POC device for INR measurement based on which therapeutic decisions were made as compared to lab monitoring of INR which is the primary aim of study. While the time within target range and the proportion of in range tests are intermediate outcomes that may be more or less highly correlated with these incidence rates. [22]

There was 1 major bleeding event in group 2 which is equal to 5% patient year while nil in group 1. The difference is however, not statically significant. Similar study done by Beyth RJ et al, showed bleeding incidence of 5.6% patient years in POC group and 12% patient year in conventional group. This study showed similar trend but high incidence which might be attributable to higher mean age of his study population (74.7 ± 6.9 years). [23]

There were 1 major thromboembolic event in each group which is also equal to 5 % patient year. In study done by Menendez et al total 20 thrombotic events occurred in conventional lab monitoring group (incidence of 5.4% patient years) and 4 in patients monitored by POC device (incidence of 1.1 % patient years) which may be because of larger sample size in their study.**Error! Bookmark not defined.**

So incidence rates for major adverse events in group managed with POC is 5% and group with lab monitoring is 10% patient year in our study, which is in the range as mentioned by various authors in patients managed by anticoagulation clinic (4.9% to 15.7% of patient-years).**Error! Bookmark not defined.**' [24, 25, 26]. However, in study done by Menendez et al major complications occurred in fewer patients in those managed with POC (2.2%) than in patients managed conventionally by lab (7.3%).**Error! Bookmark not defined.** Similar incidence of major complications with POCT monitoring 1.7% patient years in long term study done by Sawicki PT et al. [27] The reason for lower incidence may be their larger sample size as these are relatively rare events and in small sample size even a single event may show a significant increase in the overall incidence rate.

The number of minor events in our study in group 1 was 4 with incidence of 20% patient years and in group 2 was 2 and incidence of 10% patient years. In study done by Sidhu and O'Kane they followed up patients on POC for 67 patient years and had 11 minor events and had incidence rate of

16% patient year. In conventional lab monitoring they had follow up of 85.1 patient years and had 12 minor events corresponding to incidence of 14% patient year. [28] While in study done by Peter T. Sawicki incidence of minor bleeding events was 22.5% in routine lab monitoring group and 26% patient year in POCT monitoring group.**Error! Bookmark not defined.**

If we compare the incidence of bleeding events in both the groups (major+minor bleeds) there were 20% patient year bleeding events in POC group and 15% patient year in conventional group. In study done by Menendez et al 17.1% and 43.7% patients year was incidence for total bleeding events in POC and conventional group respectively.**Error! Bookmark not defined.** This higher incidence may be because of higher mean age of their study population.

Now if we consider overall incidence rate of adverse events (major+minor) it turns out to be 25% in group managed with POC and 20% patient year in conventional lab monitoring group. In study done by Sidhu and O'Kane overall incidence of total adverse events of 18% in POC group and 14% patient year in conventional lab monitoring group was detected.**Error! Bookmark not defined.**[Error! Bookmark not defined.] The pattern was similar but overall low incidence may be because of more frequent testing of almost once per week in their study. In study done by Menendez et al which has largest sample size detected an incidence of 16% in POC group and 43.7% in conventional lab monitoring group. Based on this study, sample size of present study was calculated.**Error! Bookmark not defined.**

Time in target range of INR can be considered as a surrogate marker for number of adverse events or clinical effectiveness. As in previous studies improvement in the proportion of tests or amount of time within target range has been shown to correlate with decrease in the incidence of complications[Error! Bookmark not defined.], [29] In present study the percentage of time within targetrange [30] was 59.59% in group 1 and 48.95% in group 2. This difference is statically significant. So in our study patient managed with POC were more time in target INR range than those who were managed with conventional lab monitoring. Similar results were seen in many other studies. In study done by Sawicki et al after 6 months the patients managed with POC and lab monitoring had 53% and 43.2% time in target range respectively and in study done by Beyth et al 56% and 32% respectively.**Error! Bookmark not defined.**[Error! Bookmark not defined.] In study done by kortke and Korter patient in POC group were 79% times in target range and in conventional lab monitoring group 62% times in target range.**Error! Bookmark not defined.** The higher percentage in both the group may be because they had chosen wider range of target INR (2.5-4.5) and more frequent testing. [31]

The POC group was more in TTR (59.59%) than conventional group (48.95%) still had higher incidence of adverse events though not statistically significant. Most of these events occurred while INR was out of TTR.

5. Limitations of Study

1) Sample size is marginally less than calculated statistically significant sample size. As the study period is time bound, the patient on oral anticoagulants are not so common and various exclusion criteria, sample size remained slightly lesser than required.
2) The samples were taken in non-randomized fashion so there may be selection bias.
3) Minor events were also taken into account in present study and there is a chance of missing them by patient as they can be asymptomatic and patient may not have reported them. However, this is common in both groups.

6. Conclusion

INR measurement with point of care device for monitoring of oral anticoagulant therapy is as safe, in terms of clinical effectiveness, as lab measurement by therapeutic INR control.

OAC dose adjustment based on point of care device INR result is reliable, easy to perform, relatively painless, less time consuming method for controlling anticoagulation, and also had higher percentage in the theurapeutic range, and hence, is suitable and comparable alternative to conventional lab monitoring.

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