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# ACUTE FEBRILE ILLNESS;

## DURING THE COURSE OF ORAL ANTICOAGULATION WARRANTS IMMEDIATE INR CHECK

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**ABSTRACT…** Oral anticoagulation is needed in many patients like after prosthetic valves insertion, in atrial fibrillation, clots in LA, clots in LV and DVT etc. It is mainly achieved by warfarin sodium which has many interactions with multiple other drugs and its action varies in different other chronic diseased states. **Objectives:** to see the response of acute febrile illness on the chronic stable state of INR on a fixed dose of oral warfarin sodium. **Methods:** All the patients with acutely deranged INR who had a stable and controlled INR previously and a fixed dose of warfarin sodium were admitted in the cardiac surgical ward at FIC and their history was explored and recorded. A total of 966 patients were admitted in (CSW) during the period of April, 2012 to April, 2014 with deranged INR. INR was checked twice or sometimes thrice to rule out the laboratory error. 504 patients were female & 462 patients were male, 56 patients had repeated admission for their INR control, most of them were callous regarding taking dose of warfarin so they were excluded from the study. **Result:** A total of 631 patients had low INR due to missed dose of warfarin sodium. Out of them 13 patients got stuck valve for which emergency redo prosthetic valve replacement was done. 06 patients died in emergency due to late presentation after the prosthetic valve got stuck. Only 279 patients had high INR on the previous dose of warfarin sodium, out of them 216 patients had out of range INR. They were treated by FFP transfusion and holding the Warfarin sodium dose for certain period of time.76% of the patients give H/o acute febrile states 101-103 with rigor & chills (Malaria, enteric fever, pharangitis, cellulitis, boils and UTI etc. etc.) since last 3-4 days for which they had got treatment from some local Gen. practitioners and gave the H/o bleeding gums, general body malaise, bruising, joint aches & pains. 24% of patients denied any acute febrile illness before their INR got out of range 2 patients died in emergency due to intra cerebral bleed after INR got uncontrolled. **Conclusions:** Any acute febrile illness even of short duration may cause sudden derangement of previously controlled INR on certain fixed dose of warfarin sodium which can create a life threatening situation like intra-cerebral bleed, haem-arthrosis, excessive menstrual blood loss leading to severe anemia. Other less dangerous situation are gum bleed, bruising, joint aches & pains and general malaise. So, it is always advisable and logical to get INR check when ever any acute febrile illness even of short duration is encountered to avoid grave situations.

**Key words:** Acute febrile illness, INR, Warfarin sodium, Out of range, Oral anticoagulation.

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## INTRODUCTION

Warfarin is the most commonly used oral anticoagulant in the world but it has certain limitation as well like it has a very narrow therapeutic range and drug interactions with many recently known medicines & foods .several diseased states also affect the anticoagulation effects of the warfarin. Warfarin metabolism, induction or inhibition of its anticoagulant effects, displacement of warfarin molecule from the portion binding sites thus increasing the available warfarin and decreased intestinal absorption of Vit.K are some possible mechanisms for warfarin over or under response.

Since primary liver diseases, congestion of liver due to CCF, hypothyroidism is well documented in the literature as causes of altered response of warfarin. Our study was to see the role of any acute febrile illness in causing altered response of warfarin.

As very little work is done in this regard, however some studies show that biologic "disappearance rate" of factors II, VII, IX and X was increased in a small no of patients with fever due to any cause. Pneumonia, influenza, pharangitis, enteric fever and malaria are some of the febrile illnesses that have been shown to affect the kinetics of some drugs. These findings and certain other reports in the literature strongly recommend that the role of febrile illness in regards to warfarin response in humans is urgently needed to be investigated.

## MATERIAL & METHOD

All the patients with deranged INR who had previously stable INR on certain fixed dose of warfarin were admitted in the Hospital. Their history was taken & physical examination made. Their INR was recorded in an INR chart. INR was checked on sysmex c500 machine and if ambiguity was suspected, it was repeated twice or thrice to confirm the report. Patients with their callous attitude towards the medicine intake or those who deliberately missed the dose or those who have taken over dosage as mistakenly and the patients with chronic debilitated states are excluded from the study.

Total 910 patients were included in the study after deducing the 56 callous patients from the total no of admission for deranged INR. Demographic data of the patients is summarized in Table-I.

| Total of patients (n) 910 | | |
|---|---|---|
| | **High INR (279)** | **Low INR (631)** |
| Age > 30 years | 169 | 236 |
| Age < 30 years | 110 | 395 |
| **Sex** | | |
| Male | 88 | 276 |
| Female | 191 | 355 |
| **Prosthetic valves** | | |
| MVR | 106 | 305 |
| AVR | 74 | 176 |
| DVR | 99 | 150 |
| AF | 35 | 82 |
| Stuck valves | 02 | 11 |
| H/o CVA | NIL | 19 |
| Bleeding complications | 138 | NIL |
| H/o Febrile illness | 203 | 07 |
| H/o inappropriate dosing | 93 | 307 |

**Table-I.**

## RESULTS

From the above data one thing which is quite evident is that patients with acute febrile illness had a tendency towards high INR which may sometimes rise to out of range and can complicate or endanger the life. Out of total no. of patients (n), the 203 (22%) patients had raised INR while only 07 (0.8%) patients had low INR in their acute febrile illness.

## DISCUSSION

International normalization ratio (INR) is a reliable and reproducible laboratory test to measure the coagulability of the blood in patients who are on chronic oral anticoagulation therapy due to whatever reason. But this INR is a very labile parameter which can be deranged due to variable reasons including various infective diseases, dietary habits, or other organic dysfunctions. Very little work is done in this highly sensitive and critical field but still some attempts are made to understand the causes of this high vulnerability of INR in various infective and non-infective febrile illnesses.

Landefeld et al. reported that patients with two or more co-morbid risk factors had 20 folds increased risk of bleeding as compared with patients with no co-morbid condition. The co-morbid conditions include cancer, serious cardiac illnesses, liver dysfunction, acute renal diseases, any acute febrile illnesses and severe anemia. Richards reported in 1943 that induction of fever in rats can dramatically raise the effectiveness of oral anticoagulants which were then used as a rat killer medicine. Loeliger et al. claimed in 1964 that the rate of biological unavailability of various clotting factors like factor II, VII, IX, and X was raised in various patients with febrile illness, no matter what may be the cause of fever. To the updated knowledge, we come to conclusion that well established studies have not yet been conducted on human race on a large scale basis but one can speculate that any potential link must exists between febrile illness and increased response of oral anti-coagulants (Warfarin).The reason for this raised anticoagulation response in febrile illness can only be due to any or many of

the following reasons.

- α– Decrease in the metabolism of oral anticoagulants.
- β– Increase in the clearance of Vit.K dependant clotting factors in febrile illness.
- χ– Decrease in the protein binding of the oral anticoagulants in febrile illness thus increase in bio-availability of the anti-coagulant drug.

Regarding a potential mechanism for the possible effect of acute febrile illness on response of warfarin, one possible explanation is decreased warfarin metabolism. Hepatic oxidative enzyme or cytochrome P-450 has a marker known as antipyrine[1-4]. A 36% reduction in the clearance of Hepatic cytochrome P-450 enzyme marker (Antipyrine) was reported during pneumonia[3]. Antipyrine is metabolized partly by the same P-450 isoenzyme that metabolizes warfarin (CYPIA2 [R-isomer] and CYP2C9 [S-isomer]). Endotoxin-induced fevers have also been shown to reduce the clearance of antipyrine by 35% and theophylline by 22%[2-3]. Another potential mechanism of febrile illness causing enhanced response to warfarin is increased clearance of Vit.K dependant clotting factors. Decreased protein binding of warfarin is yet another potential cause of enhanced response of warfarin in febrile illness. An in vitro study showed decreased protein binding affinity of warfarin with human serum albumin on increasing temperature[3-7]. Theoretically speaking this fact can result in transient increased response of warfarin sodium during high body temperatures due to febrile illness[6-9].

Our study has also some limitations like it is a small study, single centered study, subject is not extensively studies in developing countries where use of warfarin & febrile illness co-exist in majority of cases and most of population addressed in under educated.

## CONCLUSIONS

It is therefore advisable for all the oral anticoagulant users to remain very pertinent and well aware of their febrile illnesses as these can cause a very miserable and life threatening consequences if not taken seriously early in their course.

INR must need to be checked along with other investigations made to rule out the cause of febrile illness. General practitioners should also keep this fact in mind while dealing with a febrile patient on oral anticoagulants and should refer the patient where facility to manage such situation exists.



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"Life isn't about waiting for the storm to pass; it's about learning to dance in the rain."

Vivian Greene