

Sensitivity to warfarin following cardiac surgery

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We read with great interest the article by Tyson and colleagues entitled ‘Identification of clinical factors predicting warfarin sensitivity after cardiac surgery.’¹ The study contains valuable tips. Detecting factors influencing the control of the international normalized ratio (INR) in patients undergoing these surgeries can help to identify patients who are at greater risk and need more attention. The importance is especially due to the previous findings which showed that variation in INR following heart valve replacement surgery can affect mortality independently.²

The authors measured warfarin dose index (WDI) as a marker of warfarin sensitivity by dividing the patient’s INR at the 4th day following initiation of warfarin loading to mean dose over the preceding 3 days. The authors pointed the significant role of left ventricular ejection fraction (LVEF) and cross-clamp time during surgery with log of WDI in linear regression model.

Due to the importance of the issue and the remarkable findings of the study, we think that several points regarding the methodology of the study might worth to be mentioned. The study design was mentioned as a retrospective cohort. However, in the method section it was described that ‘participants were given a patient information sheet prior to surgery.’ Additionally, patients were included if they could consent. These descriptions regarding patient inclusion seems to be inconsistent with a retrospective design since the total process of data collection was throughout the hospital stay.

Patients included in the study were warfarin recipients following cardiothoracic surgery and their sensitivity to warfarin was studied. However, there are many underlying conditions in patients treated with warfarin, which can increase the sensitivity to warfarin, many of which were not considered among the inclusion or inclusion criteria

of the study. One of these factors is hypoalbuminemia.² Regarding the albumin serum level, it was only mentioned in the abstract section that the serum albumin concentrations ‘were collected from consenting patients.’ However, neither in the method nor the result section was this issue elaborated.

Additionally, in patients with renal insufficiency, decreased activity of cytochrome (CYP)2C9, can increase the sensitivity to warfarin. Moreover, changes in protein binding and volume of distribution of drugs as well as the slower carboxylation of coagulation factors can lead to changes in INR in these patients.³ However, the kidney function of patients do not seem to be considered. Additionally, it was previously shown that changes in thyroid function with several mechanisms can alter the response to warfarin. In uncontrolled hyperthyroid patients, the clearance of the vitamin K-dependent coagulation factor is increased. Conversely, in patients with hypothyroidism, decrease in the catabolism of coagulation factors subsequently lead to the decrease in the effect of warfarin and decrease the INR.³

Other conditions such as malnutrition and reduced dietary intake as well as chronic diarrhea have been proposed to influence the sensitivity to warfarin.⁴ So, it seems that these conditions could be mentioned among the limitations of the current study.

Drug interactions are another considerable issue in patients receiving warfarin that can affect the control of INR. The authors noted that ‘concurrent medication prescribed’ and ‘medication history’ were both documented during the study. However, the report regarding the interacting medications only mentioned amiodarone and omeprazole. It is not clearly mentioned that how antibiotic prophylaxis before surgery, which can increase the response to warfarin, was considered.

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Additionally, amiodarone which was used by some of the patients in the study can inhibit the metabolism of warfarin by inhibiting CYP2C9 and CYP1A2.⁵ The intensity and severity of this interaction is dose-dependent and the maximum effect on the metabolism of warfarin occurs several weeks after the initiation of amiodarone.^{5,6} In addition, owing to the long half-life, the effects may persist for several weeks following the medication discontinuation. The authors pointed that receiving amiodarone during the postoperative period significantly affected log WDI in the bivariate correlation but not in the linear regression. Presenting the data regarding the time of initiation of amiodarone as well as the medicine dosage could add more informative data in this regard.

Previous studies have shown a direct correlation between weight or body mass index (BMI) of patients with the dose of warfarin. It was shown that with each unit increase in BMI, the weekly needed dose of warfarin increased by 0.69 mg.⁷ In addition, in obese patients, the initial response to warfarin is reduced.⁸ The role of weight seems to be an important variable since some investigators have even adjusted the WDI by dividing it to weight in the formula.⁹ In the present study, the researchers found that patients 'weight did not have a significant correlation with log WDI.' However, this finding should be interpreted cautiously, since the mean weight of patients in this study was 81 ± 19.4 kg. Presenting the data of patient BMIs could help the readers to judge more precisely the role of obesity.

Another point is about the role of time elapsed following the surgery. It was proposed that warfarin sensitivity declines over time and the initial hospitalization carry a higher risk.² In this regard it seems that there was a variation between the included patients in the study: initiation of warfarin postoperatively was even postponed to the 18th day following surgery. This delayed onset of medication hypothetically may influence the role of cross-clamp time in warfarin sensitivity. The current literature does not provide data on this issue. However, if it was clear regarding in how many patients warfarin initiation was delayed and how their INR control was affected, valuable data could be generated. It seems that more restricted criteria could make the patient population more homogeneous.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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