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Warfarin Compliance after Mechanical AVR in the Pediatric Population: Case Series from a Developing Country

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Abstract

Background and Aim: Mechanical prosthetic heart valves exert a lifelong thromboembolic complication requiring continuous antithrombotic therapy. Vitamin K antagonist is the recommended therapy of choice along with meticulous INR monitoring to achieve and maintain an INR of 2.0 - 3.0. The study aimed to assess the compliance of anticoagulant therapy in pediatric patients after AVR and to highlight the challenges faced during follow-ups. Methods: A retrospective study was conducted at NICVD Hospital in Karachi, Pakistan for a time frame of 2 years from 2020-2021 where 7 patients were selected. Data were collected using hospital medical records and then validated through a phone call mediated structured questionnaire-based interview. Results: 2 out of 7 patients in the case series were compliant to regular follow-ups and had their INR in the desired range owing to their higher education status and access to INR clinic for regular follow-up in urban setting. Younger patients in the case series were non-compliant. 4 out of 7 patients who were on dual anti-coagulant regimens including warfarin and aspirin were either closer or within the range than compared to those on single drug regimen. Conclusion: Compliance was observed in patients who had favorable demographics and higher education. Multiple recent trials including PROACT and PROACT XA are underway to develop novel treatment options apart from warfarin after mechanical aortic valve replacement. Home-based INR testing kits provide easy access to regular testing in remote areas. Multi-center studies are required for in-depth analysis regarding reasons of non-compliance in pediatric population.

Keywords

Mechanical AVR, Warfarin, INR monitoring, Anticoagulant,

Thromboembolic

1. Introduction

Rheumatic heart disease (RHD) is a global burden that's affecting almost 33 million people mostly in low socioeconomic countries. RHD manifests in the form of carditis and valvular disorders of which mitral and aortic valves are most commonly affected. Definitive management includes transcatheter or surgical replacement of the valve [1].

Prosthetic heart valves have a lifelong risk of thromboembolic complications requiring continuous antithrombotic therapy that needs meticulous monitoring of INR throughout the lifetime. After valve replacement with a mechanical device American College of Cardiology has recommended the use of anticoagulation therapy with a vitamin K antagonist (VKA) to achieve and maintain an INR of 2.0 - 3.0 in the adult population [2] [3]. According to a meta-analysis conducted in 2019, the paediatric and adolescent populations were also maintained within INR of 2.0 - 3.0 and none developed a late hemorrhagic event [4]. Poor control of INR after mechanical and bioprosthetic AVR, subjects these patients to frequent thromboembolic complications mainly consisting of transient ischemic event, stroke and pulmonary embolism due to systemic emboli with an incidence of 1.8 and 8 events per 100 patient-years on and off anticoagulation, respectively [5].

Achieving safe and effective anticoagulation in children and adolescent is difficult owing to the difference in developmental hemostasis physiology and drug metabolism mechanism in children making patients more prone to thromboembolic complications. Dietary factors in which the most significant effect is seen with consumption of green vegetables, multivitamins or diet rich in vitamin K that suppresses the anticoagulant effect of warfarin were observed [6].

2. Case Series

A retrospective study was conducted at NICVD Hospital in Karachi, Pakistan for a time frame of 2 years from 2020-2021. RHD patients within the age group of 5 - 18 years who underwent aortic valve replacement (AVR) with Medtronic open pivot mechanical heart valve were included. Those outside this age group with non-rheumatic heart disease (congenital heart disease), with involvement of any other valve and replacement with bioprosthetic valves were excluded. The data was collected using hospital medical records and then validated by the patients or their guardian in the study after informed consent through a phone call mediated structured questionnaire-based interview. (See Table 1)

Case 1: A 6 years old girl, rural resident, diagnosed with severe aortic stenosis, bicuspid aortic valve and severe aortic regurgitation. Post AVR, She was started on warfarin 2.5 mg once daily OD. INR value on the 2nd postoperative day was

Table 1. Demographic with Post-OP and current drug regimens and INR values.

	Gender	Age at OP (Yrs.)	Weight at OP (Kgs)	Residence	Post-OP regimen	INR-2nd P.O.D	Current regimen	Latest INR	Frequency of follow-ups
Case-1	Female	6	15	Rural	Warfarin 2.5 mg OD	1.33	Warfarin 5 mg OD	3.8	Once in 6 months
Case-2	Female	9	19	Rural	Warfarin 2.5 mg OD	1.2	Non-compliant on 2.5 mg Warfarin OD	1.7	Once in 5 to 6 months
Case-3	Male	14	39	Rural	Warfarin 5 mg OD Aspirin 75 mg OD	3.1	Warfarin 5 mg OD	1.2	Once in 12 months
Case-4	Male	16	44	Rural	Warfarin 5 mg OD Aspirin 75 mg OD	2.0	Warfarin 5 mg OD Aspirin 75 mg OD	1.8	Once in 6 months
Case-5	Male	16	40	Rural	Warfarin 5 mg OD Aspirin 75 mg OD	1.4	Non-compliant on 5 mg Warfarin OD Aspirin 75 mg OD	1.8	Once in 6 to 7 months
Case-6	Male	18	52	Urban	Warfarin 5 mg OD Aspirin 75 mg OD	1.1	Warfarin 7.5 mg OD (4 days/week) Warfarin 5 mg OD (3 days/week) Aspirin 75 mg OD	2.6	Once in 3 months
Case-7	Female	18	70	Urban	Warfarin 7.5 mg OD Aspirin 75 mg OD	1.1	Warfarin 7.5 mg OD (4 days) Warfarin 5 mg OD (3 days) Aspirin 75 mg OD	2.5	Once in 3 months

1.33; her current regimen is warfarin 5 mg OD with an INR of 3.5. She was inadequately counselled regarding dietary habits having regular consumption of green leaky vegetables and lentils and poorly compliant with INR follow-ups due to illiteracy.

Case 2: A 9 years old girl, rural resident, was diagnosed with mild aortic stenosis, severe aortic regurgitation. Post AVR, she was started on warfarin 2.5 mg OD. INR value on the 2nd postoperative day was 1.2; her current regimen is warfarin 2.5 mg OD with an INR of 1.7. She was inadequately counselled regarding dietary habits and was poorly compliant having regular consumption of green leaky vegetables and lentils with INR follow-ups due to inaccessible follow-up clinics. She was non-compliant to warfarin use and used it intermittently.

Case 3: A 14 years old boy, rural resident, was diagnosed with moderate aortic stenosis, severe aortic regurgitation. Post AVR, He was started on warfarin 5 mg OD and aspirin 75 mg OD. INR value on the 2nd postoperative day was 3.1; his current regimen is warfarin 5 mg OD with an INR of 1.2. He was inadequately counselled regarding dietary habits having regular consumption of green leaky vegetables and lentils and poorly compliant with INR follow-ups due to illiteracy and lack of knowledge regarding the adverse effects.

Case 4: A 16 years old boy, rural resident, was diagnosed with severe aortic stenosis, bicuspid aortic valve, severe aortic regurgitation. Post AVR, he was started on warfarin 5 mg OD and aspirin 75 mg OD. INR value on the 2nd postoperative day was 2.0; his current regimen is warfarin 5 mg OD and aspirin 75 mg OD with an INR of 1.8. He was counselled regarding dietary habits despite having regular consumption of green leaky vegetables and lentils and importance of regular INR monitoring, but the patient was non-compliant to follow-ups due to monetary issues.

Case 5: A 16 years old boy, rural resident, was diagnosed with mild aortic regurgitation with severe aortic stenosis. Post AVR, He was started on warfarin 5 mg OD and aspirin 75 mg OD. INR value on the 2nd postoperative day was 1.4; his current regimen is warfarin 5 mg OD and aspirin 75 mg OD with an INR of 1.8. He was counselled regarding dietary habits at discharge despite having regular consumption of green leaky vegetables and lentils and was non-compliant with INR follow-ups due to inaccessible follow-up clinics and lack of knowledge.

Case 6: A 18 years old boy, urban resident, was diagnosed with moderate aortic stenosis and moderate aortic regurgitation. Post AVR, He was started on warfarin 5 mg OD. INR value on the 2nd postoperative day was 1.1; his current regimen is warfarin 7.5 mg OD/warfarin 5 mg OD alternatively with INR of 2.6. He was counselled regarding dietary habits at discharge having good adherence to consumption of meat, lentils, wheat and rice, with avoidance of green leafy vegetables and was compliant with INR follow-ups.

Case 7: A 18 years old girl, urban resident, was diagnosed with severe aortic stenosis, bicuspid aortic valve, moderate aortic regurgitation. Post AVR, she was started on warfarin 5 mg OD and aspirin 75 mg OD. INR value on the 2nd postoperative day was 1.1; her current regimen is warfarin 7.5 mg OD/warfarin 5 mg OD alternatively + aspirin 75 mg OD with an INR of 2.5. She was counselled regarding dietary habits at discharge having good adherence to consumption of meat, lentils, wheat and rice, with avoidance of green leafy vegetables and was compliant with INR follow-ups.

3. Discussion

Maintaining INR in therapeutic range is affected by several factors amongst which, the most highlighted in the literature, were level of knowledge regarding warfarin, educational status of the patient, dietary habits, demographics and compliance to regular INR follow-ups.

The patients in our case series were taking warfarin for a period of fewer than 3 years and did not manifest any bleeding or thrombotic complication, therefore, the adverse effects of warfarin complications can't be assessed. Level of knowledge regarding warfarin is mainly dependent on the patient's behavior towards compliance, which is determined by, the educational status of patient and level of counselling by healthcare professionals. Case 6 and 7 had attained higher education hence, it was noted that they were more aware and took more

interest in self-medication while having easy access to INR clinics. They were vigilant of their desired INR range, food and drug interactions, symptoms of adverse events. As compared to cases 1 to 5, who mainly lied in the pediatric age group and resided in rural areas. They were dependent on their guardians that were not well-educated. Demographics played an important role in achieving INR in the therapeutic range, as seen in cases of rural areas (cases 1 to 5) that did not have the facility of INR monitoring clinics in comparison to the patients living in urban areas (cases 6 and 7) having easy accessibility to tertiary care setups. It can also rightly be pointed out that achieving safe and effective levels of anticoagulation in children is more challenging than in adults, due to the difference in physiology and drug metabolism [7].

Dietary factors in which the most significant effect is seen with consumption of green vegetables, multivitamins or diet rich in vitamin K that suppresses the anticoagulant effect of warfarin. Cases 1 - 5 had consumption of green leafy vegetables and lentils, rarely meat, whereas, cases 6 - 7 had consumption of meat, lentils, wheat and rice and avoided green leafy vegetables.

To reduce the burden of anticoagulation after mechanical valve replacement, multiple strategies have been employed including targeting a lower INR, use of dual antiplatelet therapy (DAPT) and non-warfarin oral anticoagulants [8]. PROACT (Prospective randomization On X Anticoagulation Clinical Trial) started in June 2006 and will be completed in February 2022. It compares whether patients could be safely managed with DAPT *i.e.* (aspirin 325 mg and clopidogrel 75 mg) or lower dose warfarin versus standard warfarin in low and high thromboembolic risk groups. Primary endpoints of the study were set at minor/major bleeding episodes, thromboembolism (TE) or valve thrombosis [6]. In the low risk for TE arm patients who were randomized on DAPT therapy experienced primary end point event 29 times (10.07% per patient-year) and 13 times in the standard warfarin group (3.78% per patient-year; rate ratio: 2.66; 95% confidence interval: 1.38 to 5.12; p = 0.003). Hence, this arm of the trail was terminated in 2014 due to higher risk of TE in patients on DAPT versus warfarin therapy [6]. In the high risk arm where patient were randomized on either low-dose warfarin or standard warfarin, at 5-year interval primary endpoint events occurred 5.50% per patient-year in the low-dose warfarin group versus 9.35% per patient-year in the standard warfarin group (rate ratio: 0.59; 95% confidence interval: 0.42 to 0.82; p = 0.002). There was an overall reduction in the bleeding events in the low dose warfarin group, with no significant differences in mortality between the two groups. On the basis of interim results of this trail, FDA approved a recommendation of maintaining an INR of 1.5 - 2.0 along with aspirin 81 mg/day starting 3 months after On-X AVR [8].

Another prospective randomized trail PROACT Xa started in May 2020 with estimated study completion by July 2024, comparing apixaban with warfarin in patients with On-X AVR [9]. In ARISTOTLE trial (Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation), apixaban arm was

more effective in preventing ischemic or hemorrhagic stroke versus warfarin in patient with atrial fibrillation [10]. Similarly, a meta-analysis by Touma *et al.*, reported that compared to warfarin, apixaban showed lower risk of bleeding in patients requiring prolonged anticoagulation [11]. The results of PROACT Xa study can generate novel treatment options, apart from warfarin, for On-X AVR.

To improve compliance home-based INR testing kits should be introduced to provide hassle free regular testing in remote areas. In a study conducted in Minnesota, in-home monitoring group of patients who used a Coaguchek Xs System were compared to the in-clinic group of patients, and the results were similar in terms of time taken to achieve therapeutic range [10]. No significant difference was observed in cases of major bleeding or TE between the two groups, however, monitoring in-home is more convenient and suited to the patient as it saves resources [10]. The initial cost of the Coaguchek Xs System is high ranging in between Rs 32,000 - 40,000, however eventually it is more beneficial since one lab test costs approximately Rs 800 whereas Coaguchek Xs testing strip costs Rs 500 [12].

Our study had numerous limitations, primarily it had only 7 patients from a single hospital set up, who underwent AVR. Multi-center studies will help achieve more holistic understanding. Demographical location was another limitation where majority of our patients belonged to rural areas. Hence cohort studies will give a just comparison of the two socio-economic groups. It is also noticed that due to limited facility of INR monitoring clinics in rural areas, there's a need to invest and train the paramedical staff to cater to the patients. Lastly, INR should be strictly checked on a regular basis for patients on warfarin therapy identical to the DOTS protocol for tuberculosis.

4. Conclusion

The study evaluated the level of compliance of oral anticoagulation therapy in pediatric and adolescent population after mechanical AVR in patients with RHD. It highlights the reasons for non-compliance and provides suggestions to overcome them. It was noticed that the major cause for non-compliance was poor follow-ups to INR monitoring which can be improved with home-based INR testing kits and using recent advances in anticoagulation therapy which are not INR dependent. There is still a need for in-depth discussion to obtain more information about the reasons for non-compliance from multi-center studies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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