Thrombosis Research 134 (2014) 255–258

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Anticoagulation of cardiomyopathy in children

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ARTICLE INFO

Article history:
Received 18 June 2013
Received in revised form 8 April 2014
Accepted 6 May 2014
Available online 10 May 2014

Keywords:
anticoagulation
cardiomyopathy
children

ABSTRACT

Objectives: Cardiomyopathy is a common cause of heart failure in children. Thrombosis is a potential significant secondary complication. Thus warfarin is recommended by the American College of Chest Physicians for the treatment of children with cardiomyopathy despite the lack of published evidence to support its use.
Methods: A retrospective clinical audit to estimate the rates of major bleeding and incidence of thromboembolism associated with oral anticoagulant therapy (warfarin) for primary thromboprophylaxis in a cohort of children with cardiomyopathy. Relevant outcomes including thrombosis and major haemorrhage were defined *a priori* according to internationally accepted definitions.
Results: 36 children (35.9 warfarin years) were examined, with 25% taking warfarin for greater than 1 year. Primary reasons for discontinuation of warfarin therapy were cardiac transplantation (n = 7), transition to VAD (n = 1), improved cardiac function (n = 17), transfer of care (n = 3), change to aspirin (n = 2). The mean age at starting warfarin was 5.4 years (range 0.2-15.2). The most common Target Therapeutic Range (TTR) for warfarin therapy was 2.0 – 3.0. TTR achievement was normally distributed and occurred in a mean 48.5% of all INR tests. There were zero warfarin related adverse events, including thrombosis or haemorrhage.
Conclusion: The low rate of TTR achievement is consistent with previously reported TTR achievement rates for infants. In addition the low rate of TTR achievement was likely influenced by the clinical profile of this complicated condition in children. Nonetheless, this data shows that the clinical outcomes for this cohort are acceptable and warfarin therapy can be safe in children with cardiomyopathy.

Introduction

Cardiomyopathy is a serious condition of the myocardium and is a one of the most common causes of heart failure, and heart transplantation in children older than 1 year [1]. Dilated cardiomyopathy (DCM) is the most common type of cardiomyopathy reported in paediatric patients, accounting for more than 50% of cases, followed by hypertrophic cardiomyopathy (HCM), and restrictive cardiomyopathy (RCM) [2–4].

DCM is characterised by an "enlarged left ventricular chamber and reduced systolic ejection without an increase in left ventricular wall thickening" [2]. In contrast HCM, is an autosomal dominant disorder, which is described as "the presence of hypertrophied, non dilated ventricles in the absence of another disease that creates a hemodynamic disturbance" [4]. Finally, RCM is defined as "restrictive filling and reduced diastolic volume of either or both ventricles with normal or near normal systolic function and wall thickness" [3]. Despite the differences in pathophysiology of these cardiomyopathies, all these patients experience reduced blood flow, which subsequently gives them an increased risk of thrombosis [5,6].

There is relatively little specific data about the role of anticoagulant therapy as primary thromboprophylaxis in children with cardiomyopathy. A systematic literature review from 1980-2011 found no primary studies of the use of prophylactic anticoagulation in paediatric cardiomyopathy. Of the twelve most recent reviews describing cardiomyopathy in children, only one mentioned the use of anticoagulants [3]. This review suggested the use of anticoagulation on the basis that children with cardiomyopathy are at increased risk of thromboembolic events but quoted no primary studies into the safety and efficacy of anticoagulation [3]. Similarly, the American College of Chest Physicians, recommend the use of anticoagulants in the treatment of cardiomyopathy on the basis of its common use in adults [7] however they cite no primary studies

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http://dx.doi.org/10.1016/j.thromres.2014.05.007
0049-3848/

into its safety and efficacy in paediatric populations when used for this indication.

The aim of this paper was to conduct a retrospective audit of the medical records of children receiving warfarin for cardiomyopathy to estimate the rates of major bleeding and the incidence of thromboembolism.

Method

This retrospective audit was conducted at the Royal Children's Hospital (RCH), Melbourne, Australia from September 2011 until February 2012. The inclusion criteria were: Children aged ≤ 18 who were taking warfarin for the indication of cardiomyopathy between the 1st January 2004 and the 31st of December 2010. Children receiving any concomitant anticoagulation or ventricular assist devices, or children whose cardiomyopathy or warfarin was not managed at RCH were excluded.

This study obtained institutional ethics approval (HERC 31211A). No written consent was required from study participants, due to the retrospective nature of this audit. The study did not involve any contact with patients or their families.

Potential patients were identified via the RCH's INR and cardiomyopathy databases. A two stage process to data collection was then applied. Data from the INR database was exported onto an excel spreadsheet to determine per patient and for the population: the total number of INR tests, mean INR result, and the proportion of INRs within the patients Target Therapeutic range (TTR). Cluster analysis of the whole sample's INR results was used to determine the sample target therapeutic INR range (TTR) achievement [8].

The cardiomyopathy database and medical records of all identified patients were audited to identify any evidence of warfarin related adverse events such as major bleeding or reduced bone mineral density, and radiological or clinical evidence consistent with thromboembolic events. Reviewing both of these data bases as well as medical records ensured that data collection encompassed all inpatient admissions, emergency department visits, outpatient appointments as well as clinical investigations. As this was a retrospective study, the researchers could not dictate when echocardiography was performed.

Other clinical data collected from patient unit records included: type of cardiomyopathy, date of birth, date of diagnosis, gender, weight, and concurrent medications.

A definition of a major bleed (adapted from Schulman 2005) was determined *a priori* in order to determine which bleeding events should be classified as a major adverse event [9]. Thus major bleeds were defined as:

- The bleeding resulted in a fatality.
- The bleeding occurred in a critical region or organ ie. Intracranial or retroperitoneal.
- The bleeding led to a significant and unexpected drop in haemoglobin levels, of 20 g L^{-1}, (1.24 mmol L^{-1}) or more, or any bleed which required a transfusion.
- the bleeding required the patient to be admitted to the emergency department for a period greater than 24 hours, or admitted as an inpatient.

We also *a priori* determined that a reduction in bone density would be classified as significant if a Z score of less than or equal to -1.0, was reported on a bone mineral density scan.

The statistical software package SPSS Version 20 was used in this study for data processing and analysis.

Results

Thirty six children (18 male and 18 female) were identified as being treated with warfarin thromboprophylaxis for the indication of cardiomyopathy who satisfied the inclusion criteria. Twenty eight children had DCM (77.8%), four had RCM (11.1%), three had HCM (8.3%) and 1 had left ventricular non compaction (LVNC) cardiomyopathy (2.8%). Of these patients, thirty one (86.1%) were in congestive heart failure at the time of presentation. The Left Ventricular End Diastolic Score was able to be retrospectively determined in 20 of the patients with DCM, and was found to have a median of 6 (Range = 3.6-8.3). Furthermore, 25 of the patients with DCM had a median Left ventricular ejection fraction of 24.0% (Range = 10-45, normal range = 55-75).

These patients contributed 1293 INRs and 35.9 warfarin years, with only 25% (n = 9) of children taking warfarin for a period greater than 1 year. Table 1 shows the primary reasons for warfarin discontinuation for the purposes of this study. At the conclusion of the study, 5 patients continued on warfarin therapy. There were 2 deaths within this cohort in the study period, neither related to the warfarin therapy. One child died due to complications post cardiac transplantation, having previously ceased anticoagulation. The other child transitioned to ECMO and LVAD, and then died shortly after. Further, the transfer of two children from warfarin to aspirin was due to increased ventricular function in one patient and was unable to be retrospectively determined in the other patient. There were zero haemorrhagic or thrombotic adverse events documented in these patients.

Examination of other known warfarin related adverse events revealed four of the patients who were on warfarin for greater than one year and tested for osteopaenia as per standard clinical practice, showed reduced bone mineral density in at least one site. Table 2 shows the reductions in bone density in these patients on examination.

All children except for one had a Target Therapeutic Range (TTR) of 2.0 – 3.0, the other child had a TTR of 2.5-3.5. TTR achievement was normally distributed and occurred in a mean 48.5% of all INR tests, and 51.3% of all tests in children over the age of 2 years. Fig. 1 depicts the percentage spread of INRs across the population which were below, within and above the target therapeutic range. The mean age of children starting warfarin was 5.4 years (range 0.2-15.2). 19.4% (n = 7) of all patients studied were under the age of 1 at the time of commencing warfarin. 80.6% of patients (n = 29) had INR results within their TTR greater than 30% of the time.

Discussion

Cardiomyopathy is a severe illness of childhood, with potentially fatal outcomes [2–5,10–13]. Many children may resolve after a period of intensive supportive medical therapy, while others will require cardiac transplantation, directly, or after bridging via ECMO or VAD [1–3,11]. In either circumstance it is critical to avoid secondary complications such as thromboembolism [3,5,6,14,15]. Routine anticoagulation with vitamin K antagonists has been advocated, but there is no data to support the safety or efficacy of this approach [7,14]. We report a consecutive series of children, who routinely received warfarin thromboprophylaxis for cardiomyopathy, and demonstrated that it was safe and effective, despite a relatively low rate of target range achievement. There were no bleeding or clotting complications during the study period. While larger studies would be beneficial, our data supports the use of routine anticoagulant primary prophylaxis for children with severe cardiomyopathy.

This study examined the safety and efficacy of warfarin thromboprophylaxis in a cohort of children with cardiomyopathy. The fact that 86.1% of the patients were in congestive heart failure at the time of presentation as well as the extensive reductions seen in Left ventricular ejection fraction, end diastolic scores, and fractional shortening Z scores demonstrates the severity of the cardiomyopathy in these children. The efficacy of warfarin thromboprophylaxis in preventing thrombosis in this cohort was measured by looking at echocardiography results with no patients found to have a thrombotic event whilst on warfarin therapy. The safety of warfarin use in this cohort was