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Oral anticoagulant therapy interruption in children: A single centre experience

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ABSTRACT

Background: The use of anticoagulant therapy in paediatrics is common, with vitamin K antagonists remaining the most commonly prescribed therapy. There is a weak evidence base behind many of the recommendations for anticoagulant therapy in paediatric patients. One of the areas requiring further research is the management of anticoagulant therapy interruption. Interruption to anticoagulation is the period surrounding a planned invasive procedure whereby long term anticoagulation is ceased, and recommenced post procedure. The word bridging refers to the use of low molecular weight heparin or unfractionated heparin to anticoagulate during the period of sub therapeutic INR. To date institutional protocols for bridging anticoagulation are based on adult guidelines. However, there are currently no studies validating the extrapolation of these guidelines to paediatrics. This study seeks to review the clinical outcomes associated with current bridging practices employed at a tertiary metropolitan children's hospital.

Methods: The patient population was selected from the warfarin management registry of a Clinical Haematology service of a major metropolitan children's hospital. The admission history of these patients was queried to identify admissions where anticoagulation interruption would typically be required. Namely, these were dental extraction, cerebral or cardiac angiography, or cardiac catheterization. Data relating to demographics, anticoagulant therapy interruption plan, and clinical outcomes were recorded.

Results: A total of 61 admissions for children aged between 1 year and 17 years and 11 months were analysed for this study. Congenital heart disease (CHD) was the primary underlying disease for which long-term oral anticoagulation with warfarin was indicated. Children with Moyamoya in this cohort were treated more consistently compared to the other disease groups. There were no instances of major bleeding ($n = 0$) or thrombotic events ($n = 0$).

Conclusion: This study describes the current practices and outcomes associated with anticoagulant therapy interruption at one institution thereby filling an evidence gap in the paediatric anticoagulant management. It achieved this by analysing the largest and most representative cohort to date. This project is a stepping stone from which future studies of safety and efficacy of paediatric anticoagulation interruption management can be developed.

1. Introduction

The use of antithrombotic agents in the paediatric setting is becoming increasingly common [1,2]. The agents most commonly used in children are vitamin K antagonists (VKA), unfractionated heparin (UFH), and low molecular weight heparin (LMWH) [2]. The indications for anticoagulation in the paediatric setting are markedly different to that of adults. The most common reason for anticoagulation is for primary thromboprophlyaxis in the setting of congenital cardiac disease [3,4]. This is commonly for a single ventricle with a Fontan circuit, mechanical heart valve or dilated cardiomyopathy. Many of the recommendations governing antithrombotic use in children are supported by a weak evidence base which is particularly evident in the area that surrounds interruption to therapy [5].

While there is a lack of a universally accepted definition [6], bridging anticoagulation refers to the administration of subcutaneous LMWH, or intravenous UFH to compensate for a sub-therapeutic international normalised ratio (INR) due to interruption of VKA therapy. Interruption of oral anticoagulation in a child is needed for a variety of reasons. The most common reason is for an invasive investigation or procedure and

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interruption is needed to decrease the risk of major bleeding. The majority of data in adult populations relating to anticoagulant therapy interruption is drawn from observational studies, rendering the evidence base for such management relatively weak (Grade 2C) [6,7]. The Bridge trial [8], a randomised double-blind placebo controlled study, recently published in adults with atrial fibrillation on warfarin, demonstrated no difference to thrombotic events with cessation of warfarin alone. In that study, Douketis et al also demonstrated an increased risk of bleeding, with an event rate of 3.2% in the bridged group, compared with 1.3% in the no-bridging group. A recent update on consensus guidelines for warfarin reversal, divided the patient population into low and high risk, and supported only bridging those who are high risk [7]. The overall trend in adult guidelines for interruption to anticoagulation appears to be shifting away from initiation of bridging therapy, apart from those who are high risk for thrombotic complications.

In children the evidence is markedly poor, as the only published study on paediatric bridging is an observational study published in 2012 [9]. The study by Moruf et al., whilst adding to the limited literature in paediatric anticoagulation interruption, had several issues that preclude its transference to other paediatric centres. This study followed a conservative bridging regime, was a study only of adolescents (mean age 17.5 years) and was limited to 23 bridging events. The primary reason for anticoagulation was venous thromboembolism (VTE), provoked or spontaneous, with no congenital cardiac malformations. The lack of data in this area appears to be prompting clinicians to treat all the patients as "high risk", and bridge with LMWH even though the bleeding risk of this has not been established. The emphasis appears to fall to prevention of further VTE, rather than prevention of iatrogenic bleeding [9].

This study aims to add to the current knowledge base by generating descriptive data relating to the clinical outcomes associated with periprocedural interruption of oral anticoagulation in children.

2. Methods

The patient population was selected from the warfarin management registry of a Clinical Haematology service at a major children's hospital in Melbourne, Australia. Children in this registry are those who require warfarin therapy and have been referred to the haematology service for management. For inclusion in the initial participant pool patients needed to have a target therapeutic range for warfarin of an INR > 2. Additionally, for a given admission to be included in the study the primary procedure carried out had to be one of cardiac catheterisation (diagnostic or therapeutic), cerebral angiography, or dental extraction, as oral anticoagulation is typically interrupted for these procedures. All eligible admissions between January 2006 and December 2013 were included. Admissions were excluded if the patient was aged 18 years or older at time of admission and if the interruption to warfarin therapy was triggered by reasons other than the procedures of interest. There are 61 admissions which represents 57 unique patients. The primary outcomes of interest were major bleeding events and thrombotic events. For this study we adopted the definition of major bleeding for surgical studies as approved by the Subcommittee on Control of Anticoagulation of the ISTH (18). To summarise, major bleeding in this study is considered to be 1) Fatal bleeding and/or 2) Symptomatic bleeding or bleeding into a critical site and/or 3) Extra-surgical site bleeding causing a fall in haemoglobin of >20 g/L in a 24 h period or requiring transfusion of two or more units of whole blood or red cells and/or 4) Surgical site bleeding requiring a second intervention and/or 5) Unexpected or prolonged surgical site bleeding. Thrombotic events were defined as new deep vein thrombosis (DVT), or pulmonary embolism (PE) presenting with clinical signs and/or symptoms, including thromboses within the Fontan circuit.

Fig. 1 depicts the process of participant selection and recruitment to this study.

All data were collected retrospectively through review of both electronic and hard copy medical records for each admission. Sources

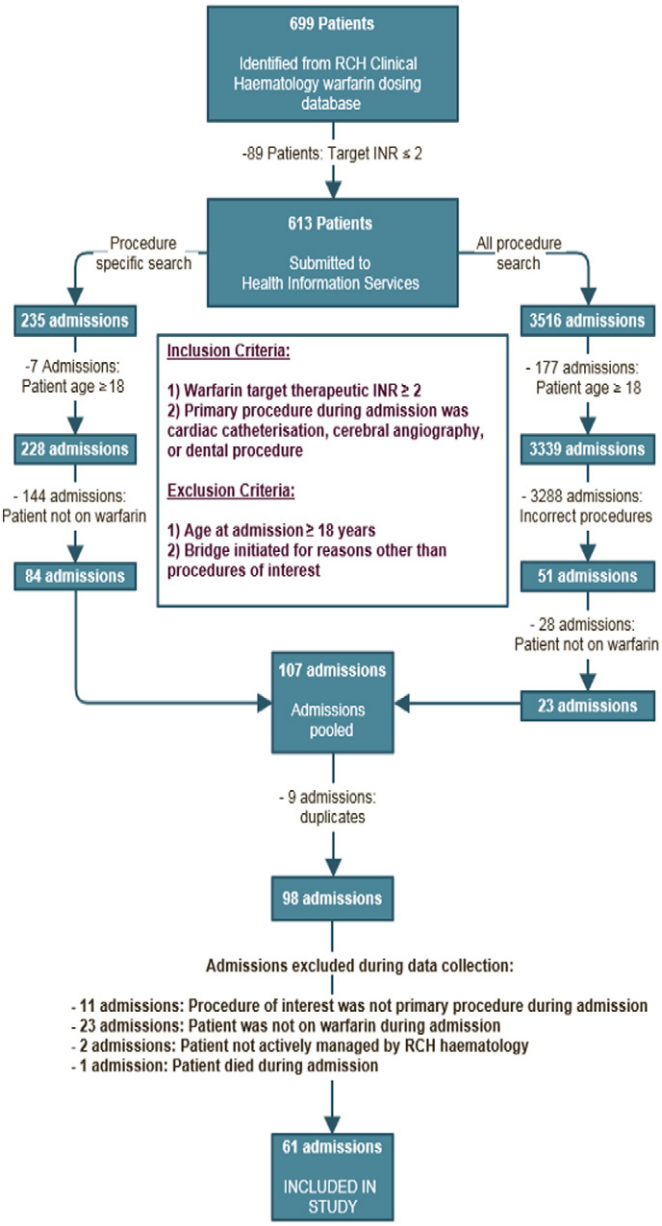

Fig. 1. Process of participant selection and recruitment to this study

within medical records were primarily inpatient medical notes but correspondence, discharge summaries, medication charts, and fluid charts were also used.

The following information was recorded for all eligible participants: gender; date of birth; primary indication for warfarin; warfarin target INR range; dates of warfarin cessation and restart; clinical outcomes. For admissions where bridging anticoagulation was instituted the details of the pre-procedure and/or post-procedure bridging protocol were identified and recorded. Namely these were: duration of pre-procedure and/or post-procedure treatment; anticoagulant agent used; dose.

Statistical analysis consisted of generating descriptive statistics. Normality was determined by the results of the Shapiro–Wilk test conducted using the Analysoft StatPlusMac package. Normally distributed continuous data are reported as a mean ± SD, and medians (range) are used to report non-normal continuous data. Summaries of categorical data are presented as frequency values and percentages.