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ORIGINAL ARTICLE

Safety and Efficacy of Warfarin Therapy in Remote Communities of the Top End of Northern Australia

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Background Warfarin remains a widely used anticoagulant but application in the remote context is not well documented. This study aimed to assess in more detail whether warfarin is being utilised effectively in Australia's most isolated and remote areas.

Methods Retrospective cohort analysis of 2013 captured international normalised ration (INR) results from people engaged in long term warfarin usage within a number of remote Northern Australian communities. Assessment of monitoring, effectiveness of dosing and complication rates was undertaken.

Results A cohort of 167 patients was established. On average, warfarin was utilised within therapeutic range 52% of the time. Monitoring frequency averaged 16 days. Major bleeding and thrombo-embolism occurred at rates of 5.8 and 4.1 per 100 patient years respectively.

Conclusions Therapeutic utilisation of warfarin in this setting is close to accepted rates but has room for improvement. Monitoring was acceptable and complication rates were not disproportionately high. This study indicates that warfarin is being used with reasonable safety and efficacy in remote regions, but further research is needed.

Keywords Warfarin • International normalised ratio • Anticoagulation • Rural • Remote • Indigenous health

Introduction

Warfarin is a Vitamin K antagonist which has been utilised as an anticoagulant for over 70 years [1]. Despite the introduction of a newer generation of oral anticoagulants, it is likely to remain extensively used world-wide, with proven efficacy for a variety of clinical indications. Unfortunately, warfarin has a narrow therapeutic window, requiring close monitoring using a standardised measure—the International Normalised Ratio (INR)—to avoid dramatic fluctuations. Inter-patient dose variability, interaction with other medications and dietary vitamin K make achieving steady state

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complex, and time spent in a pre-determined therapeutic window remains around 64% [2]. However, several studies report averages closer to 50% [1,3–5].

This is noteworthy as sub-therapeutic administration increases the risk of treatment failure, whilst supra-therapeutic dosing carries a risk of major haemorrhage. Understandably, the limitations of warfarin make it a challenging medication to adapt to a rural context due to isolation and distances involved to access pathology services and specialised staff [6]. The introduction of accurate point-of-care INR testing devices has aided monitoring [6,7].

The top end of Australia's Northern Territory has extremely remote living conditions with an average population density of less than one person per square kilometre and high Aboriginal Australian representation [8]. Local populations have a significant burden of chronic disease, notably among the highest rates of rheumatic heart disease in the world [9]. Warfarin remains the predominant anticoagulant in this setting, as the newer novel anticoagulants have yet to demonstrate efficacy in prosthetic valve replacements and valvular atrial fibrillation [10].

There is concern that warfarin is being used sub-optimally in the rural setting [11], however some studies have disputed this [5,12]. We aimed to assess in more detail whether warfarin is being adopted effectively in Australia's more remote regions, in particular where there was a significant Indigenous Australian contingent.

Methods

Study Design

The study aimed to demonstrate efficacy of warfarin utilisation via several approaches. Firstly, whether patients were being monitored regularly. Secondly, objective quantification of the proportion of time spent in pre-determined therapeutic dose ranges. Finally, analysis of treatment complication rates represented by occurrence of haemorrhagic and thromboembolic events. Haemorrhage was categorised as mild or severe, which was further characterised as non-fatal or fatal. Severe haemorrhage was defined as any of: admission to hospital; transfusion of two or more units of blood; death; or intracranial bleeding.

Study Population

This was a retrospective cohort analysis of data collected from 1 January 2013 to 31 December 2013 of patients who were utilising warfarin in communities within the top end of the Northern Territory of Australia that were remote and very remote based on Australian Standard Geographical Classification. One community, classified as outer regional, was also included. The research was cleared by the Ethics Committee of the Northern Territory Government Department of Health and Menzies School of Health Research (QAAR 2014-2190).

The identified cohort was included irrespective of indication for anticoagulation, demographics and comorbidities. However, patients met exclusion criteria if information on target INR range and indication were not available or there was no evidence of planned or active long-term warfarin use (>12 months). Patients were also required to have at least two dated INR results for analysis.

Data Source

Initial data was drawn from the Northern Territory health care database, Primary Care Information System (PCIS). This is the main primary public health platform available in the majority of top end rural and remote communities and could be readily interrogated. Initially, all recorded INR results and prescriptions for warfarin documented in the PCIS database were captured. 215 patients were identified across 23 communities (see Figure 1) with a collective total of 3998 point-of-care INR results. Seventeen of these communities were classified as very remote, five as remote and one as outer regional, although the last was considered to be more reflective of a remote setting.

Individual demographics including age, gender, remoteness classification and ethnicity were documented along with indication for warfarin therapy, target therapeutic range, comorbidities and any concomitant anti-platelet medication. Forty-eight patients met the exclusion criteria, leaving 167 eligible for the study. Gaps in information were corroborated with the main electronic cardiology database available in the region, NT Cardiac. Additional information sourced in this manner included aetiology of atrial fibrillation if present, type and position of mechanical valve/s if present, target INR range, cardiac function and cardiovascular comorbidities.

All INR readings were separated by patient to calculate individual mean, median, minimum and maximum results. Furthermore, total days in the study, total INR readings, average length of time between readings and type of testing device were also recorded. Further analysis was conducted to calculate time below, within and above therapeutic range. Finally, data was reviewed to ascertain how often patients met the accepted minimum INR monitoring of at least one INR result per month [13]. Patient records were screened for documented complications potentially related to warfarin therapy and all INR results over five were actively reviewed.

Patient information was cross referenced with the electronic data bases utilised at the sole tertiary and two secondary referral hospitals in the region—Royal Darwin Hospital, Katherine District Hospital and Gove District Hospital respectively. Databases utilised were Clinical Work Station and Caresys, linking all the hospitals via a combined interface. All electronic data including file notes, clinic letters, emergency department visits and hospital discharge summaries were reviewed for all potential complications relating to warfarin therapy. This was further correlated with clinical information analysis of hospital coding for potential severe warfarin related presentations using the ICD-10-CM classification system (D68, I60, I61, I62, I63, I64, T82). All complications identified by any of these methods were reviewed in detail including perusal of hard copy hospital inpatient notes to

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