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Does warfarin-related intracerebral haemorrhage lead to higher costs of management?

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ABSTRACT

Background and purpose: Warfarin-related intracerebral haemorrhage is associated with significant morbidity but long term treatment costs are unknown. Our study aimed to assess the cost of warfarin-related intracerebral haemorrhage.
Methods: We included all patients with intracerebral haemorrhage between July 2006 and December 2011 at a single centre. We collected data on anticoagulant use, baseline clinical variables, discharge destinations, modified Rankin Scale at discharge and in-hospital costings. First year costings were extracted from previous studies. Multiple linear regression for treatment cost was performed with stratified analysis to assess for effect modification.
Results: There were 694 intracerebral haemorrhage patients, with 108 (15.6%) previously on warfarin. Mean age (SD) of participants was 70.3 (13.6) and 58.5% were male. Patients on warfarin compared to those not on warfarin had significantly lower rates of discharge home (12.0% versus 18.9%, $p = 0.013$). Overall total costs between groups were similar, $AUD 25,767 for warfarin-related intracerebral haemorrhage and $AUD 27,388 for non-warfarin intracerebral haemorrhage ($p = 0.353$). Stratified analysis showed survivors of warfarin-related intracerebral haemorrhage had higher costs compared to those without warfarin ($AUD 33,419 versus $AUD 30,193, $p < 0.001$) as well as increased length of stay (12 days versus 8 days, $p < 0.001$). Inpatient mortality of patients on warfarin was associated with a shorter length of stay ($p = 0.001$) and lower costs.
Conclusion: Survival of initial haemorrhage on warfarin was associated with increased treatment cost and length of stay but this was discounted by higher rates and earlier nature of mortality in warfarinised patients.

1. Introduction

Stroke morbidity is associated with estimated direct healthcare costs of AUD $2 billion per year in Australia [1]. Intracerebral haemorrhage (ICH) represents between 8 and 15% of all strokes in Western societies, and is responsible for 12% of the total stroke costs [2–4]. In Australia, this cost was estimated at AUD $232 million per year [1,5]. The relative high cost of ICH is attributable to the high morbidity with which it is associated, with 52% of survivors permanently moving into a nursing home [1,6–9].

The use of oral anticoagulant therapy (OAT) for stroke prevention (most commonly in patients with atrial fibrillation) increases both the risk for ICH and its severity [10,11]. Other known major predictors of poor outcome in ICH include haematoma volume, intraventricular extension and infratentorial location [9,12–18]. Approximately 5–12% of ICH is related to warfarin therapy [11,15,19]. Patients with atrial fibrillation on warfarin have an annual incidence of ICH of approximately 0.3% [19,20]. This is likely to increase given the expected increase in the prevalence of atrial fibrillation in an ageing population. For example, in the US, the proportion of warfarin-related ICH increased from 5.8% in 2005 to 7.3% in 2008 [21–24].

Recently, novel irreversible anticoagulant agents have become available for stroke prevention among patients with atrial fibrillation. A recent meta-analysis of randomised trial data estimated that compared to warfarin, new oral anticoagulants were

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associated with a relative risk of 0.45 (95% CI 0.31–0.68) for ICH and 0.49 (95% CI 0.36–0.66) for all intracranial bleeding [25–28]. Therefore the higher costs of novel agents may be offset by reduced incidence of OAT-associated ICH. While the societal impact of increased morbidity and mortality is established, the treatment cost of warfarin-related ICH is unknown. Evidence of effective treatments remains largely confined to intensive blood pressure control and reversal of anticoagulation, with little benefit to overall outcomes [29–34].

The aim of the present study was to investigate the costs of warfarin-related ICH. We hypothesised that warfarin-related ICH was associated with increased costs compared with non-warfarin related ICH.

2. Materials and methods

2.1. Study setting and participants

Participants for our study were sourced from a prospectively maintained database of stroke patients admitted to the Royal Melbourne Hospital (RMH) Comprehensive Stroke Centre, a quaternary metropolitan service. All cases with confirmed diagnosis of primary ICH between July 2006 and December 2011 were included in the study. Information regarding patient demographic characteristics, premorbid function (assessed using modified Rankin Scale [mRS]), comorbidities (hypertension, atrial fibrillation, ischaemic heart disease, previous stroke and diabetes) and warfarin use were ascertained during the admission interview [35–37]. Stroke characteristics, such as stroke subtype (haemorrhagic or ischaemic) and side (left or right hemisphere, brainstem or multiple site) were determined from clinical assessment and imaging tests. Data was drawn from a local institutional review board approved prospectively collected clinical database on all patients presenting to RMH Comprehensive Stroke Centre.

2.2. Clinical and cost outcomes

Major outcomes considered in this study included stroke costs (in-hospital costs, first year out-of-hospital costs, and total costs), functional status (discharge destination and discharge mRS), and in-hospital mortality. In-hospital costs were obtained from the Clinical Costing Unit of RMH, which records itemised costs for all in-patient encounters. First year out-of-hospital costs were based on discharge destination, with costs estimates derived from the North East Melbourne Stroke Incidence Study (NEMESIS), using a method we have previously published [8,38]. In-hospital costs and first year out-of-hospital costs were summed to obtain total costs of stroke over 12 months.

2.3. Statistical analyses

Patients were classified into two groups according to history of warfarin use: non-warfarin ICH (non-w-ICH) and warfarin-related ICH (w-ICH). Continuous variables and categorical variables were analysed using the Student's *t*-test and chi squared test, respectively. Logistic regression was used to determine the effect of warfarin on the prediction of disability (mRS 4–6). Age and pre-admission mRS were used as covariates. Multiple linear regression analysis was performed using log-transformed 1-year cost as these are known to be positively skewed [39]. For variables to be included in the multivariable analysis, the significance level for univariable analysis was set at 0.20. The significance level for evidence of interaction was set at 0.01. The following factors were considered: warfarin use, age, sex, atrial fibrillation, smoking status, diabetes, hypertension, ischaemic heart disease, previous stroke, inpatient death, pre-admission mRS and stroke location. These factors were selected on the basis of clinical work and previous studies [4–6,9,12,15,16,40–43]. Duan's retransformation estimator was used when retransforming estimated costs from the multiple linear regression log model [44]. To account for bias inherent in retransformation of beta coefficients when using log-transformed cost, a smearing estimator was calculated. This was 1.49 for the reduced multivariate model. Analyses were performed using SPSS version 20.0 and SAS 9.3.

3. Results

3.1. Patients

Baseline characteristics of the two groups are described in Table 1. A total of 710 patients were admitted with confirmed ICH between 1 July 2006 and 31 December 2011. Of these, complete data on demographic profile, presentation details, warfarin status, outcomes and costs were available for 694 (97.7%) patients, of whom 108 (15.6%) were taking warfarin. The mean (SD) age of study participants was 70.3 (13.6) years and 58.5% were male. Patients on warfarin were significantly older and had significantly more comorbidities (Table 1).

3.2. Clinical outcomes

Warfarin use was associated with worse outcomes among ICH patients, with 39.8% inpatient hospital mortality in the w-ICH group compared to 24.7% in the non-w-ICH group ($p = 0.001$) (Table 2). Discharge destinations were also significantly different between non-w-ICH and w-ICH patients ($p = 0.013$): 18.9% and 12.0%, respectively, were discharged home. Furthermore, patients with non-w-ICH tended to have better discharge function, with 523 (89.2%) having an unfavourable discharge mRS (mRS = 2–6), compared to 103 (95.4%) patients in the w-ICH group ($p = 0.058$). Median length of stay (LOS) did not differ significantly between the two groups, 6 days for w-ICH versus 7 days for non-w-ICH ($p = 0.352$).

3.3. Costs

Crude comparisons revealed no differences between the w-ICH and non-w-ICH groups in terms of median costs of the index admission $AUD 10,215 and $AUD 8874 ($p = 0.720$) nor median 1-year costs ($AUD 25,767 and $AUD 27,388, $p = 0.353$) (Table 2).

3.4. Prediction of disability

Warfarin and age were significant predictors of disability post ICH when adjusted for each other and preadmission mRS. Warfarinised patients had a significantly higher chance of being disabled post ICH than those not (Table 3). Premorbid function did not appear significant in predicting disability in ICH.

3.5. Multivariable analysis of cost

From the results of the univariable analysis (not shown), age, death, warfarin, ischaemic heart disease, previous stroke and hypertension were selected for inclusion in the multivariable model (Table 4). Multivariable analysis showed significant association between 1-year costs and age, warfarin use and death. The model also included an interaction variable between warfarin and death. Increasing age was associated with cheaper costs, while warfarin was associated with higher costs.