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Surgical workload, risk factors and complications in patients on warfarin with gastrointestinal bleeding

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ABSTRACT

Introduction: This study aimed to assess surgical workload and risk factors for gastrointestinal bleeding in patients on warfarin admitted to a hospital.

Methods: Data was collected for all warfarinised patients admitted between April 2005 and October 2007 with gastrointestinal bleeding.

Results: A total of 30 patients (average 80 years) were recorded. Indications for warfarin therapy were atrial fibrillation (80%), mechanical heart valve (6.67%) and embolic disease (13.33%). Fifty percent were admitted with an INR above therapeutic range and of these patients, 83% were on one or more medications known to potentiate the anti-coagulation effect of warfarin. Nine patients were also taking anti-platelet medication. Five of these nine had an admission INR within the intended therapeutic range. Thirteen patients received blood transfusions and had a significantly higher ($p < 0.05$) INR (average 9) than the 17 patients not requiring transfusion (average 2.8). The average cost of transfusion per patient was £470. None of the patients required acute surgical intervention. The average length of stay was 7 days, at a total cost of £1444 per patient. Investigations found the cause of bleeding to be diverticulosis in 9 patients and neoplastic disease in 4 patients. Almost half of the patients received no investigation due to risks from co-morbidity.

Conclusions: Uncontrolled anti-coagulation, polypharmacy and age were overwhelming risk factors for major gastrointestinal bleeding. Our results show that adding anti-platelet therapy has to be clearly justified against the increased risk of bleeding. Cost to the surgical department was high and no patients required surgical or radiological intervention.

What is already known about this topic?: Warfarin is an important drug, but the complications of its use are difficult and expensive to deal with. Warfarin use is a risk factor for haemorrhage, and this commonly involves the gastrointestinal tract. The use of warfarin is set to increase as the population ages and atrial fibrillation and other cardiovascular risk factors become more prevalent. Consequently, one can expect a rise in warfarin-related gastrointestinal haemorrhage.

What does this article add?: Our study aimed to assess the burden of gastrointestinal haemorrhage secondary to warfarin on our surgical department (which was high), and also to assess what the risk factors for haemorrhage for patients on warfarin. One of the risk factors we uncovered was polypharmacy, particularly involving anti-platelets e.g. aspirin. We highlight the need for further guidance with regards to managing patients on warfarin, and suggest possible solutions to the problems uncovered.

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1. Introduction

The prevalence of atrial fibrillation (AF) increases with age, occurring in less than 1% of the population under 60 years and in almost 10% of the population over 80 years.¹ This is projected to rise with an aging population and as the prevalence of cardiovascular risk factors increases.² AF is recognised as an independent risk factor for stroke, increasing the risk by five-fold.³ Long-term anti-coagulation

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with warfarin reduces the relative chance of thrombo-embolic stroke by approximately 65%.⁴ This compares to a more modest reduction of 20% when aspirin is used alone.⁵ The National Institute for Health and Clinical Excellence (NICE) guidelines for the management of AF currently recommend the use of warfarin for the prevention of thrombo-embolic stroke.⁶ This should be considered against the annual risk of haemorrhage which is estimated at 9%.⁷ Most commonly, bleeding complications involve the gastrointestinal (GI) tract⁸ and, invariably, patients are often categorised as part of the surgical case-load.

The aims of our study were to establish the risk factors for gastrointestinal bleeding in patients on warfarin therapy and to assess surgical workload, cost and patient outcome in a single district general hospital.

2. Methods

All the case notes of patients taking warfarin admitted to the surgical assessment unit with gastrointestinal bleeding were retrospectively reviewed over an 18-month period (April 2005–October 2007). In our trust, any patient with upper gastrointestinal bleeding is admitted to the surgical department if they are over the age of 65. All lower GI bleeding is admitted to the surgical department at any age.

For each patient, the following were recorded: gender, age, the indication for warfarin therapy, discharge and admission international normalised ration (INR), concomitant medications, blood transfusion, any reversal agent requirement, investigations undertaken, alcohol intake, liver function tests on admission, and the total length of stay and cost of admission. All statistical comparisons were made using the Mann Whitney U test.

3. Results

A total of 30 patients were included in our study (16 females and 14 males) with an average age of 80 years (range = 63–93 years). AF was the indication for warfarin in 80% of patients with the remainder either anti-coagulated for recurrent thrombo-embolic events or metallic valve replacements. There were a wide range of INRs on admission (average of 5.5), with half of the patients in our study exceeding the target upper limit on admission (Fig. 1).

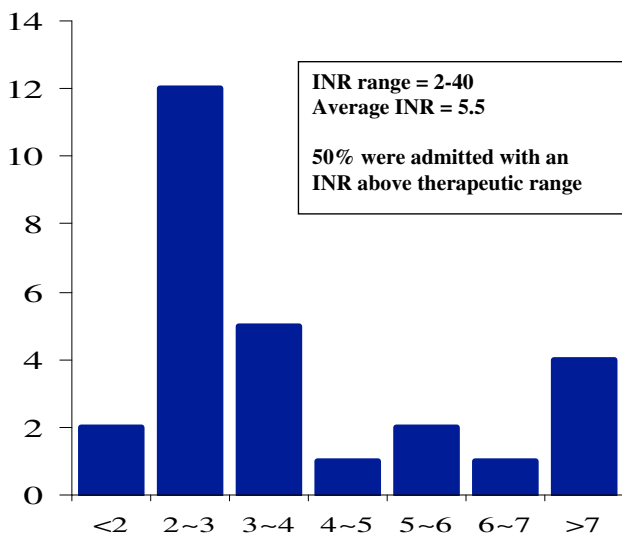


Fig. 1. Anti-coagulation at presentation. This table shows the range of INR on presentation for patients in our study. For AF, therapeutic INR = 2–3; for metallic valves, = 3–4.

Thirteen patients (43.3%) required a blood transfusion. The average admission INR of these patients was significantly higher than in those patients who didn't require a transfusion (9 vs 2.8, $P=0.02$) (Fig. 2).

Fourteen patients required the use of a reversal agent in keeping with the British Committee for Standards in Haematology.⁹ Patients requiring a reversal agent had a significantly higher INR compared to those who did not (8.2 vs 2.9) ($P=0.014$) (Fig. 3).

In thirty percent of our subjects (9 patients) it was not appropriate to carry out further investigation into the cause of their bleeding due to their extensive co-morbidity. Lower gastrointestinal studies were undertaken for the majority of patients (17 patients) and 4 patients underwent upper endoscopy as appropriate to the presentation (Fig. 4). Nine patients were diagnosed with diverticular disease as the cause of their bleed and neoplastic disease was the cause in four patients. In the remainder, no significant cause was found. No patient required surgical intervention or angiography during their acute admission to stop their bleeding.

The length of stay ranged from 1 day to 21 days (average 7 days) (Fig. 5). All patients were initially admitted to the Surgical Assessment Unit at a cost of £325 per day. The cost for stay in a general surgical ward is £190 per day giving an average cost of £1444 per patient. The cost of 1 unit of blood in our trust is £139. The mean number of units of blood used over all 30 patients was 3.4, at an average cost of £430 per patient.

Eighty-three percent of the patients were on one or medications which are known to potentiate the anti-coagulant effect of warfarin. Examples of these were amiodarone, PPI's, steroids, thyroxine analgesics e.g. paracetamol, anti-microbials and diabetic medication e.g. gliclazide. Nine patients were on aspirin or clopidogrel, as well as warfarin.

One patient had a weekly alcohol intake greater than 21 units. We found that documentation of alcohol intake was poor; either not quantified, or not recorded at all.

There was no significant data collected regarding liver function tests on admission for any of the patients.

4. Discussion

Previous studies have identified age as a major risk factor for gastrointestinal bleeding. This was confirmed by our study with an average age of 80 years. A prospective observational study by Hylek et al showed that cumulative incidence of major haemorrhage in patients over 80 years was 13.1 per 100 person-years. In patients younger than 80, it was much less at 4.9. All the patients requiring prothrombin complex – only indicated in major bleeds⁹ – in our study were over the age of 80, again highlighting the risk of major haemorrhage with increasing age. The risk of stroke, however, also

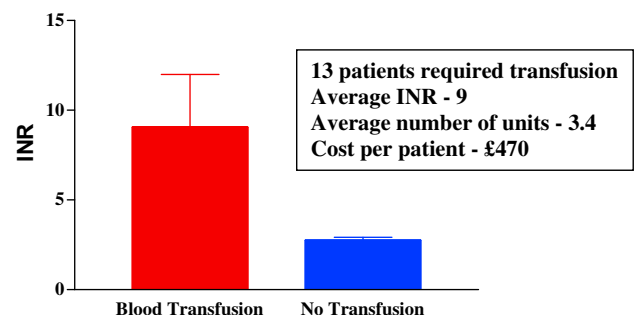


Fig. 2. Transfusion requirements. 13 patients (43.3%) required transfusion. The INR of these patients was significantly higher = 9.06, as shown by this t-test.

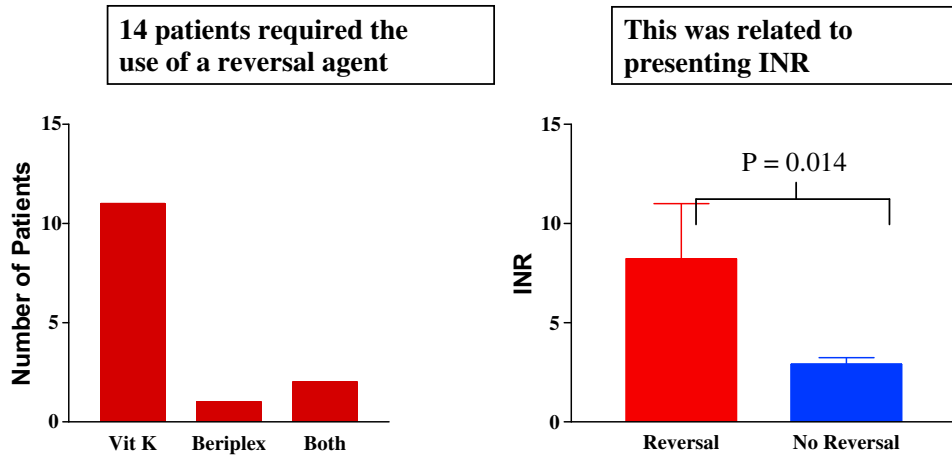


Fig. 3. Use of reversal agents. Vitamin K was the most commonly used reversal agent. Use of reversal agent was related to INR.

increases with age¹⁰ making it a difficult balance between the risk of bleeding and stroke prevention.

Currently, the British Committee for Standards in Haematology recommends that the INR is checked weekly after commencing warfarin, until it is stable, it can then be checked less frequently. It does not suggest that this should be done more frequently for patients older than 80 years. Given the increased risk of major haemorrhage, more regular monitoring of INR would perhaps be beneficial for this age group.

Polypharmacy is common with elderly patients. It is not unusual for patients to be on medications that interact with warfarin. For example, 7 patients in this study were on amiodarone. Four of these patients had INRs greater than 3.5 on presentation (3.5–6). Often this polypharmacy is unavoidable – warfarin and amiodarone are often both required in the management of atrial fibrillation – and temporary e.g. anti-microbials. The Committee also recommended that patients on any medication which may interact with warfarin should have their INR checked more regularly.⁹ The number of supra-therapeutic INRs that might be secondary to drug interaction in this study would suggest this is not always being done.

The use of anti-platelet agents i.e. aspirin and clopidogrel, in conjunction with warfarin needs justification. Half of the patients in our study did not have an elevated (and therefore falsely reassuring) INR but still presented with GI bleeding - nine of these patients were co-prescribed an anti-platelet agent. A population-based, retrospective case-control study by Delaney et al showed that the risk of haemorrhage from the gastrointestinal tract was greatly increased where anti-platelets and anti-coagulants were combined.¹¹ A recent Lancet Neurology review suggested that the

only indications for combined anti-platelet and anti-coagulation therapy are mechanical valves, AF with acute coronary syndrome, and AF with recent percutaneous coronary intervention.² None of the 9 patients on warfarin and aspirin in our study matched these criteria. A recent meta analysis has also shown that combining aspirin with warfarin is only indicated for patients with mechanical heart valves, and that the risk of major bleeding is higher in this situation in comparison to use of just aspirin or just warfarin.¹² It should be pointed out that there are no guidelines concerning the use of warfarin and anti-platelets in combination.

The risk of becoming over anti-coagulated is clearly raised by age and polypharmacy. Unsurprisingly, we found that patients with a supra-therapeutic INR are more likely to suffer haemorrhage, require transfusion and reversal agents. None of these patients required any acute surgical intervention, and yet remained under the care of the surgeons for their entire stay. We suggest that patients who present with gastrointestinal haemorrhage be triaged medically for treatment of coagulopathy and initial investigation. Acute referral to a surgical team should only be made for large bleeds or clinically unstable patients.

A large number of patients were not investigated because of their age and co-morbidity, but where possible, further investigation should always be carried out as emphasised by the diagnosis of 4 previously occult neoplasms. It is essential that GI haemorrhage is not dismissed as being secondary to over anti-coagulation only.

Diverticular disease was found in a number of patients and is known to be more common with increasing age, with some studies showing the prevalence to be as high as 60% in patients over 80

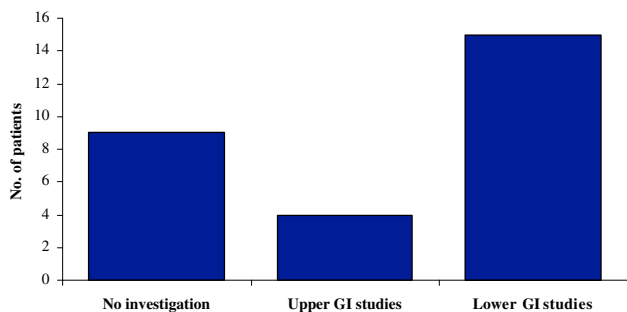


Fig. 4. Investigations used. Nine patients did not undergo further investigation due to low severity of bleed, co-morbidities or frailty.

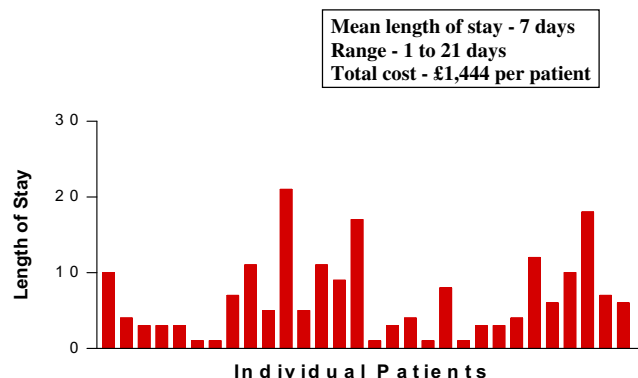


Fig. 5. Length of hospital stay. The length of hospital stay for each patient.

years of age.¹³ Whilst the majority of patients with diverticular disease remain asymptomatic, around one-fifth will suffer complications, including haemorrhage.¹⁴ Anti-coagulant use has been identified as a significant risk factor for this and warfarin should be used with caution in this group of patients.¹⁴

Excessive consumption of alcohol is known to affect warfarin metabolism and lead to raised INRs. Documentation of this important risk factor was poor in our study. A thorough social history can identify underlying habits that may be causing over anti-coagulation.

Various risk factors for warfarin associated bleeding have previously been identified but no prediction rules for physicians have been verified. The risk models that have been produced also identify age and anti-platelet use as significant variables, as well as hepatic and renal impairment, and diabetes mellitus.^{15,16} However, none of the patients in our study were found to have deranged liver function tests on admission, though this does not rule out the presence of liver dysfunction in these patients.

Ideally, data on all patients taking warfarin during the study period should be collated as a denominator, and those who suffered gastrointestinal bleeding should be compared with those who did not, and hypothesised risk factors should be analysed – however, this sort of data collection was not feasible, and thus our report is an observational one only.

Warfarin is an important and useful drug. The evidence for warfarin rather than aspirin in anti-coagulation is overwhelming. When warfarin is not suitable, however, i.e. patients at high risk of haemorrhage, it should certainly be considered. Aspirin at doses of 325 mg has been shown to significantly reduce risk of stroke in patients in atrial fibrillation,¹⁷ especially in those aged less than 75 years. However, aspirin is not available in this dose in the United Kingdom.⁶ The search for new alternatives to warfarin is ongoing. Ximelagatran, a direct thrombin inhibitor, has been shown to be superior to warfarin for post-operative prophylaxis of venous thromboembolism¹⁸ and is as effective in the prevention of stroke.¹⁹ Although the risk of bleeding complications with ximelagatran was not significantly different to that with warfarin, there are less dietary or pharmacological interactions, and the need for continuous dose adjustment is avoided. However, the side effect of hepatotoxicity has led to its discontinuation. Research into similar drugs such as dabigatran is ongoing and there is also work underway on other vitamin K antagonists such as acenocoumarol and anti-platelet agents like triflusal, which is not available in the UK. It is hoped the use of these newer agents may reduce the complications and subsequent cost associated with warfarin use.

Author contributions

Robin Som: Conceived and designed study; collected, analysed and interpreted data; drafted article; revised article; corresponding author

James A Gossage: Analysed and interpreted data; statistics; revised article

Anna Crane: Collected and analysed data; revised article

Paul H Rowe: Revised article; approved article

Conflict of interest

The authors declare that there are no potential conflicts of interest.

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Ethical approval

None declared.

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