ANTICOAGULATION & INTRACRANIAL BLEEDS - MANAGEMENT OF THE ANTICOAGULATED PATIENT PRESENTING WITH INTRACRANIAL HAEMORRHAGE

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Patients who develop intracerebral haemorrhage (ICH), whilst anticoagulated, are at high risk of dying or suffering severe disability. Provision of best possible management for these patients has a major influence on their functional outcome.

Self assessment

1. Which, if any, of the following patients, who were on therapeutic anticoagulants and suffered a significant but non-fatal spontaneous intracerebral haemorrhage, would you reverse to a normal international normalised ratio (INR)?

   (1) Those with a previous history (more than 6 months ago) of deep vein thrombosis (DVT)
   (2) Those with a previous history (more than 1 year ago) of pulmonary embolus (PE)
   (3) Those with chronic, stable atrial fibrillation (AF)
   (4) Those with paroxysmal AF
   (5) Those with a metal aortic or mitral heart valve

2. What would you use to correct the coagulopathy? *(Choose any that apply)*

   1. Fresh frozen plasma (FFP)
   2. Intravenous vitamin K
   3. Oral vitamin K
   4. Prothrombin complex concentrate (PCC) eg Beriplex, Octaplex
   5. Factor VIIa
   6. Other……..

3. In which of the following patients, if any, would you commence intravenous heparin or therapeutic low molecular weight heparin (LMWH) in the first 96 hours post presentation?

   a) Previous history of DVT (> 6 months ago)
   b) Previous history of PE (> 12 months ago)
   c) Chronic, stable atrial fibrillation
   d) Paroxysmal AF
   e) A prosthetic heart valve

4. When, following ICH, would you restart oral anticoagulants?

   - Within 48 hours
   - Between 48 and 96 hours
   - Between 96 hours and 1 week
   - Between 1 and 2 weeks
   - After 2 weeks

5. In which of the following patients would you restart oral anticoagulation once the acute event had passed? *(Choose any that apply)*

   a) Previous history of DVT (> 6 months ago)
   b) Previous history of PE (> 12 months ago))
   c) Atrial fibrillation (chronic stable)
   d) Paroxysmal AF
   e) Prosthetic heart valve

The answers to the self assessment questions are found in the text of the article.

Introduction

Warfarin is an oral vitamin K antagonist that is used to treat and prevent thromboembolic diseases. Major haemorrhage as a result of long-term oral anticoagulation occurs in 1 to 5% of patients per year. This incidence increases with patient age, duration of therapy and with degree of anticoagulation.

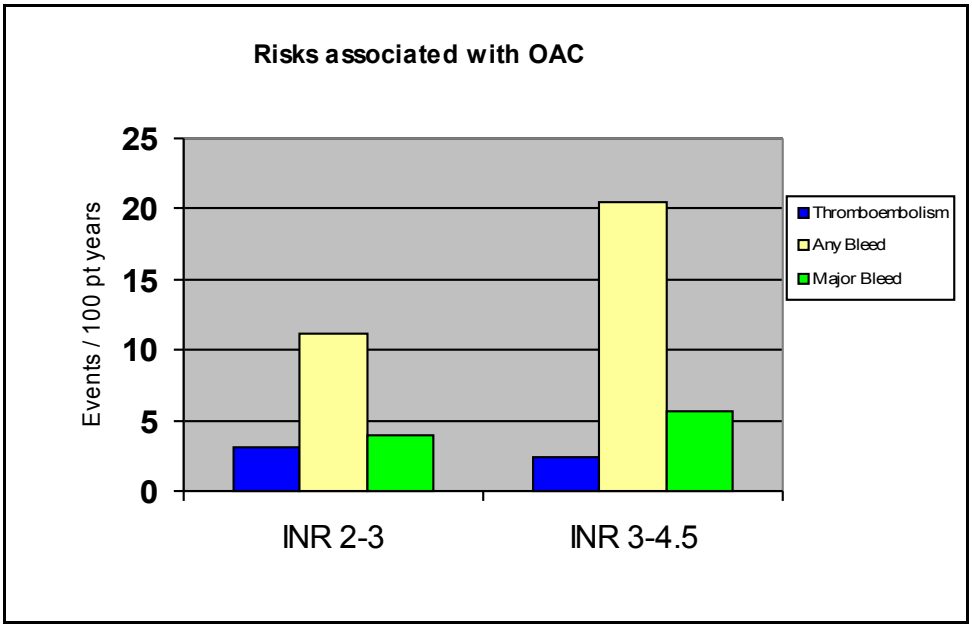
Spontaneous intracerebral haemorrhage (SICH) is one of the most feared complications of long-term anticoagulation. Patients who are anticoagulated not only suffer SICH eight to ten times more frequently than their non-anticoagulated counterparts, but also have a mortality as high as 67%, more than twice the non-anticoagulated population.[1,2] This is related to the larger haematoma size on presentation and the faster rate of haematoma expansion, both of which are associated with increased mortality.

Management guidelines

1. Prevention

Optimising INR control to within the desired range (usually 2-3) reduces the risk of ICH development. Oral anticoagulation (OAC) should be discontinued in patients in whom there is no proven indication. For patients with mechanical heart valves (MHV), the lowest effective target INR should be chosen to match valve thrombogenicity and other patient risk factors (figure 1).[3]

Figure 1: *Risks of bleeding and thromboembolism, whilst taking oral anticoagulants with different target INR ranges.*



2. Reversal of anticoagulation

Non-anticoagulated patients with intracerebral haemorrhage, have an improved survival and functional outcome when haemostatic therapy is initiated early (within four hours of bleeding). It has been suggested that, in a similar way, rapid reversal of the INR could limit haematoma expansion and improve outcome in warfarin associated intracerebral haemorrhage.[4-6] The current literature, albeit largely retrospective, supports early correction of the coagulopathy in these patients.[7-9]

The management of a bleeding anticoagulated patient presents a potential therapeutic dilemma, in which the need to reverse the coagulopathy is considered against the risk of thromboembolic consequences related to the underlying co-morbidity. **However, the need to reverse the coagulopathy and halt the intracerebral bleeding overrides all other considerations.**

Warfarin inhibits the action of vitamin K within the liver, where it acts as a cofactor in the production of prothrombin (factor II) and factors VII, IX and X. Treatment options for reversing a coagulopathy include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) and recombinant factor VIIa. A recommended guideline for reversal is shown in Table 1.[10]

Intravenous vitamin K should be administered to all patients who are warfarinsed and who suffer a SICH. It is necessary to support endogenous synthesis of clotting factors, is easy to administer, and has an effect that lasts beyond the relatively short half lives

of FFP and PCC, hence producing a sustained correction of the coagulopathy. The time of onset of oral vitamin K is too slow to be therapeutically useful in this situation.

Table 1: *Guideline for reversal of warfarin in spontaneous intracranial haemorrhage, Derriford Hospital, Plymouth, UK.* [10]

Guideline for reversal of warfarin in SICH		
5-10 mg IV vitamin K **plus** Prothrombin Complex Concentrate (PCC)		
Dose of PCC:	*INR*	*Dose*
	2.0-3.9	25 IU/kg
	4.0-6.0	35 IU/kg
	>6.0	50 IU/kg

Fresh frozen plasma contains all coagulation factors in a non-concentrated form and has been the most widely used method for coagulation factor replacement. However, recent evidence has demonstrated that FFP is less effective than PCC in correcting coagulopathy and this particularly relates to achieving a haemostatic concentration of factor IX. In addition, FFP takes time to administer - not only does it need to be compatibility tested and thawed before use, but the large volumes required may lead to difficulties with fluid overload. In addition, FFP carries risks associated with transfusion of any blood product, including allergy, blood-borne infection and transfusion related acute lung injury.

Prothrombin complex concentrate contains prothrombin, coagulation factors VII, IX and X, protein C, protein S, and protein Z. They are formulated in a concentrated form and do not require compatibility testing or thawing before use.

3. Re-anticoagulation

Decisions about reinstitution of oral anticoagulants should be based on analysis of the individual patient risk of increasing haematoma size, balanced against risk of thrombus formation and embolisation. Studies have suggested that 54% of haematomas in anticoagulated patients go on increasing in size in the initial period after presentation, compared with 16% in non-anticoagulated patients.[11]

Some advocate cautious use of intravenous heparin, or subcutaneous low molecular weight heparin in patients at high risk of thromboembolism.[12] Others suggest that the use of heparin as a bridging therapy cannot be recommended.[13]

The perceived risk of embolisation resulting in major stroke or death with a mechanical heart valve is generally overestimated. The true risk is 4% per year and the risk of valve thrombosis is 1.8% per year. The daily risk of valve thromboembolism has been calculated from this data to be 0.016% or a 2-week risk of 0.2-0.4%.[13] Compared with the increased mortality and morbidity associated with

early haematoma expansion, the available evidence supports withholding all forms of anticoagulation until the acute event has passed.[14] In high risk cases, for example mechanical heart valves, oral anticoagulation should be restarted once the acute episode has stabilized, but in low risk cases such as non-paroxysmal atrial fibrillation, the risk of re-instituting oral anticoagulants probably outweighs the potential benefit.[15]

Summary [16, 17]

Early and aggressive reversal of INR to within the normal range with vitamin K and prothrombin complex concentrate improves outcome.

- Risk of systemic embolisation in the acute phase, **even in patients with mechanical heart valves**, is low and temporary cessation of oral anticoagulation for 8-15 days is safe.
- Risk of recurrent haemorrhage after careful reintroduction of oral anticoagulation is low.

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