When should you restart anticoagulation in patients who suffer an intracranial bleed who also have a prosthetic valve?

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Abstract

A best evidence topic in cardiac surgery was written according to the structured protocol. The question addressed was about the best time to restart anticoagulation in patients with intracranial bleed with a prosthetic valve in situ. This difficult clinical decision has to balance the risk of thromboembolism during the period that the anticoagulation was reversed and later withheld vs the risk of haematoma expansion or rebleed if the anticoagulation was started early. Altogether, more than 80 papers were found using the reported search, of which 10 represented the best evidence to answer the clinical question. There were two prospective studies and eight retrospective studies. There were no randomized controlled trials on this topic. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Seven studies reported the strategy of reversal of anticoagulation with vitamin K, fresh frozen plasma or prothrombin concentrate. The emphasis was on prompt initial reversal of anticoagulation; however, the best agent for reversal was not defined. Four studies dealt exclusively with intracranial bleed in patients with prosthetic valve in situ. The remaining six studies on intracranial bleed had only a subset of patients with a prosthetic valve in situ. The anticoagulation was restarted with heparin and later switched to oral anticoagulant. Thromboembolic events during the period of reversal and cessation of anticoagulants were low (5%) as was the incidence of rebleed or haematoma expansion (0.5%). We conclude that anticoagulation can safely be withheld for a short period, up to 7–14 days in a patient with intracranial bleed with a very low probability of thromboembolic phenomenon. In patients with prosthetic valves, in situ anticoagulation in the form of heparin can safely be restarted as early as 3 days and switched to oral anticoagulation in the form of warfarin at 7 days without major concerns of bleeding.

Keywords: Mechanical/prosthetic valve • Oral anticoagulant • Intracranial haemorrhage

INTRODUCTION

A best evidence topic was constructed according to the structural protocol as described in the ICVTS [1].

THREE-PART QUESTION

[in Patients with a prosthetic valve who had an intracranial hemorrhage] what is the optimal [timing of starting anticoagulation] in order to reduce the risk of [valve thrombosis].

CLINICAL SCENARIO

Over the course of a 2-year period at our multidisciplinary team meetings, 3 patients with prosthetic heat valve (PHV) on oral anticoagulant (OAC) presented with intracranial haemorrhage (ICH); OAC was stopped and anticoagulation ceased. There were several discussions about the timings of restarting anticoagulation, and as no agreement could be reached, we resolved to consult the literature on the subject.

SEARCH STRATEGY

We analysed the published literature on (Mechanical or Prosthetic Valve on Oral Anti-Coagulant) AND (Intra Cranial Hemorrhage) using MEDLINE. Studies published between June 1985 and June 2011 were included.

SEARCH OUTCOME

Eighty-four papers were found using the reported search. Of these, 10 papers were identified, which provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

Ananthasubramaniam et al. [2] retrospectively studied 28 patients with ICH (3 had PHV in situ). They concluded that the risk of thromboembolism is low in patients with PHV when OAC is withheld following a major haemorrhagic episode. Although definite recommendations regarding the duration of safely withholding OAC could not be made, ~2 weeks of withholding

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Table 1: Best evidence papers

<table>
<thead>
<tr>
<th>No.</th>
<th>Author, date, journal and country</th>
<th>Study type</th>
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<th>Study type</th>
<th>Patient group</th>
<th>Management</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ananthasubramaniam et al. (2008), Chest, USA [2]</td>
<td>Retrospective (level III)</td>
<td>3 of 28 patients with ICH</td>
<td>Mitral: 1</td>
<td>All reversed with FFP and one with vitamin K and OAC started on 15 ± 4 days with no thromboembolic phenomenon</td>
<td>Follow-up for 6 months with two deaths (acute event). One death at 4 months at home with unknown reason (on ASA)</td>
<td>All patients’ OAC stopped and safely started without any valve-related complication</td>
<td>Safe to withhold OAC and can be started in ~2–3 weeks of time</td>
<td></td>
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<tr>
<td>2</td>
<td>Babikian et al. (1988), Stroke, USA [3]</td>
<td>Retrospective (level V)</td>
<td>6 patients with ICH</td>
<td>Prosthetic site not reported</td>
<td>Treatment strategy not reported OAC started on mean of 19 days with no thromboembolic phenomenon</td>
<td>Follow-up for 6 months with one death due to bacterial endocarditis</td>
<td>All patients’ OAC stopped and safely started without any valve-related complication</td>
<td>Safe to withhold OAC and can be started in ~2–3 weeks of time</td>
<td></td>
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<tr>
<td>3</td>
<td>Butler et al. (1998), Br J Haematol, Scotland [4]</td>
<td>Retrospective (level III)</td>
<td>16 patients with ICH</td>
<td>Mitral: 7</td>
<td>Treatment strategy not reported OAC started on mean of 7 days and 10 patients received iv heparin from day 3</td>
<td>Follow-up for 23.5 months with two deaths due to acute event and two deaths in follow-up, one with neurological sign and other suffered myocardial infarction</td>
<td>All patients’ OAC stopped and safely started without any valve-related complication</td>
<td>Safe to withhold OAC for short period and can be started in ~1 week with target. INR on lower side has definite advantage of no recurrent bleeding may be on cost of thromboembolism</td>
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<tr>
<td>4</td>
<td>Leker et al. (1998), Neurology, Israel [5]</td>
<td>Prospective (level V)</td>
<td>4 patients with ICH</td>
<td>Prosthetic site not reported</td>
<td>All reversed with FFP and vitamin K. All patients given heparin within 24 h except one whom it started after 36 h, with no thromboembolic phenomenon</td>
<td>Followed up till discharge with clinical and repeat CT scan. No death or valve-related complication</td>
<td>All patients’ OAC stopped and were safely given heparin without any complication</td>
<td>Safe to withhold OAC and early institution on heparin is safe and effective</td>
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<td>5</td>
<td>Phan et al. (2000), Arch Neurol, USA [6]</td>
<td>Retrospective (level III)</td>
<td>52 patients with ICH</td>
<td>Mitral: 14</td>
<td>All reversed with FFP and vitamin K. All patients given heparin or warfarin from 1 to 4 weeks with one thromboembolic complication</td>
<td>Followed up for 30 days with 22 deaths not related to valve-related complication</td>
<td>All patients’ OAC stopped and safely OAC or heparin started without any valve-related complication</td>
<td>Safe to withhold anticoagulant for a brief period, i.e. 7–28 days with a median of 10 days</td>
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<tr>
<td>6</td>
<td>Wijdicks et al. (1998), Neurosurgery, USA [7]</td>
<td>Retrospective (level III)</td>
<td>39 patients with ICH</td>
<td>Mitral: 16</td>
<td>Most of them reversed with FFP, and some of them given vitamin K. All patient started on OAC on median of 8 days (2 days to 3 months) with 5 patients received heparin</td>
<td>Followed up for &gt;3 months with 14 deaths of which 13 were due to acute event and 1 after 3 years following haemorrhage</td>
<td>All patients’ OAC stopped and safely OAC started without any valve-related complication and 5 patients were also given heparin</td>
<td>Safe to withhold anticoagulant for a brief period, i.e. 2–90 days with a median of 8 days</td>
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<tr>
<td>7</td>
<td>Claassen et al. (2008), Arch Neurol, USA [8]</td>
<td>Retrospective (level III)</td>
<td>12 of 48 patients with ICH</td>
<td>Aortic: 8</td>
<td>Reversal treatment strategy not reported, 12 patients started on OAC on median of 10 days (7–28 days)</td>
<td>Followed up for 43 months with two deaths in patients where OAC not restarted, one CCF and one comorbidity and one myocardial infarction</td>
<td>All patients’ OAC stopped and safely OAC started in 10 without any valve-related complication, excluding 2 deaths which were not related to valve or ICH</td>
<td>OAC can be safely withheld in patients with ICH for a short duration like 7–28 days but reinstitution of OAC definite advantage of preventing unnecessarily thromboembolic complication</td>
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Continued
anticoagulation and subsequently restarting anticoagulation seemed to be associated with no thromboembolic events.

Babikian et al. [3], from a retrospective study of 6 patients with ICH, concluded that the timing of restarting anticoagulation should be individualized and based on the assessment of both the specific risk factors related to the valve and potential causes leading to haemorrhage. An average waiting period of 19 days proved to be safe.

Butler et al. [4] retrospectively studied 16 patients with ICH and confirmed that short-term discontinuation of OAC is safe in patients with PHV. Restarting anticoagulation as early as 3 days and switching to OAC on Day 7 does not result in a high rate of recurrent fatal haemorrhage in the 2-year period after the initial intracranial bleed. Leker et al. [5] prospectively studied 4 patients with ICH. From their study, they concluded that anticoagulation is generally contra-indicated in patients with intracerebral haematoma; however, in patients with PHV, it may be dangerous to withhold such therapy because of the possible risk of thromboembolic complications. Heparin can be started as early as within 36 h after haemorrhage to prevent thromboembolic complications without any risk of increasing haematoma. In the study, the haematomas receded in all patients according to follow-up CTs, and none had thromboembolic disorder.

Phan et al. [6], from a retrospective study of 141 patients with ICH (52 had PHV), concluded that discontinuation of OAC therapy for 1–2 weeks has a low probability of thromboembolic events in patients at high embolic risk. This should be taken into consideration when deciding whether to continue or discontinue anticoagulation in these patients. Early recurrence of ICH is uncommon.

Wijdicks et al. [7] retrospectively studied 39 patients with ICH. The duration of discontinuation of anticoagulation varied from 2 days to 3 months (median 8 days). None had a thromboembolic event. No recurrence of ICH was observed during hospitalization and reinstitution of anticoagulation or antiplatelet agents. They concluded that temporary interruption of anticoagulation therapy seems to be safe and discontinuation for 1–2 weeks should be sufficient to observe the evolution of a parenchymal haematoma and to intervene if needed.

### Table 1: (Continued)

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Author, date, journal and country</th>
<th>Study type (level of evidence)</th>
<th>Patient group: Prosthesis, ICH location</th>
<th>Management</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>8</td>
<td>De Vleeschouwer et al. (2005), Acta Chir Belg, Belgium [9]</td>
<td>Prospective (level III)</td>
<td>30 of 108 patients with ICH, Mitral: 9 Aortic: 14 Tricuspid: 2 Multiple: 5 ICH location not reported</td>
<td>Reversal treatment strategy used vitamin K, FFP and PCC but not uniformly used. Nineteen patients restarted on OAC with median interval of 11 days, and all of them received LMWH day after stabilization or surgery.</td>
<td>Followed up for 12 months with 23% mortality and thromboembolic complication reported in 1 patient in the form of myocardial infarction (not due to valve thrombosis).</td>
<td>All patients’ OAC stopped and safely OAC started in 19 of 1 patient reported to have complication.</td>
<td>OAC can be safely withheld in patients with ICH for ≥3 weeks safely with urgent reversal of coagulopathy and reinstitution of OAC on priority basis.</td>
</tr>
<tr>
<td>9</td>
<td>Bertram et al. (2000), J Neurol, Germany [10]</td>
<td>Retrospective (level III)</td>
<td>10 of 15 patients with ICH, Mitral: 5 Aortic: 4 Double: 1 Cerebellar: 2 Hemispheric: 2 SAH: 2 Thalamic: 2 Temporal: 2</td>
<td>All reversed with PCC, FFP and vitamin K. All patients were started on heparin on full dose except 1 where low dose given.</td>
<td>Followed up till discharge with no mortality and four complications (two rebleeding and two cerebral infarctions) in infarct patient 1 was on low-dose heparin and other heparin was withheld for surgical point of view.</td>
<td>All patients’ OAC stopped and were started on heparin in 1–3 days with four complications.</td>
<td>Safety of withdrawal of anticoagulant for &gt;1 week in acute management of ICH cannot be maintained as guideline but reinstituting full-dose heparin in high-risk patient for thromboembolism is must ones INR has normalized and no surgical contraindication.</td>
</tr>
<tr>
<td>10</td>
<td>Kawamata et al. (1995), Surg Neurol, Japan [11]</td>
<td>Retrospective (level III)</td>
<td>20 of 27 patients with ICH, Prosthetic site not reported ICH location not reported</td>
<td>All reversed with PCC, FFP and vitamin K. All patients were given heparin soon after haemorrhage was under control and OAC started to all from day 3 to 30 days.</td>
<td>Follow-up not clearly defined with five total mortality in whole series (including those without prosthetic valve in situ) and one thromboembolic complication.</td>
<td>All patients’ OAC stopped and were started on heparin as haemorrhage was controlled and OAC started to all from day 3 to 30 days with one complication.</td>
<td>OAC needs to be stopped immediately following ICH with rapid reversal of same, keeping in view early reinstitution of anticoagulant in the form of heparin and OAC keeping in myocardial infarction and the risk benefit ratio of thromboembolism and bleeding.</td>
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</table>

Claassen et al. [8] retrospectively studied 48 patients with ICH (12 patients with PHV). Their clinical data indicate that recurrent OAC-associated ICH is uncommon when anticoagulation is resumed, whereas the risk of thromboembolic events may be comparatively greater in patients who do not reinitiate OAC therapy. However, the clinician deciding whether to restart anticoagulation after an episode of ICH should weigh other factors, including the patient risk factors for systemic haemorrhage like previous episodes of bleeding from extracranial sites (e.g. gastrointestinal tract) and other risk factors including liver and renal disease, hypertension, cancer and stroke. Patients without these risks may benefit from reinstatement of OAC therapy.

De Vleeschouwer et al. [9] from a prospective study of 108 patients with ICH (30 had PHV) estimated the overall risk of thromboembolic complications to be 0.66 events/1000 patients at risk. OAC can be stopped safely for a considerable period, with a very low overall thromboembolic event rate. The recurrent bleeding risk after restarting anticoagulation is low. In their study, recurrent bleeding mostly occurred before restarting anticoagulation and was probably caused by insufficient or unsustainable correction of the initial coagulation deficit. Immediate reversal of anticoagulation provides the patient with the best possible treatment options including surgery.

Bertram et al. [10] did a retrospective study of 15 patients with ICH (10 with PHV) and concluded that in the acute management of patients with ICH with urgent need for anticoagulation, withdrawal of anticoagulation treatment for >1 week is not safe. However, full-dose intravenous heparin therapy may be restarted at 7 to 10 days after the onset of INR over the embolism, provided that early, active and sustained normalization of INR over the first week of the acute illness is necessary.

Kawamata et al. [11] retrospectively studied 27 patients with ICH (20 had PHV) and demonstrated that patients with anticoagulant-related haemorrhage may undergo surgery and anticoagulants can be resumed after an interval of 3-30 days. Aggressive surgery should particularly be performed in patients with anticoagulation-related chronic SDH or subcortical haemorrhage, as in the cases of anticoagulant unrelated ICH.

Broderick et al. [12] published guidelines for the management of spontaneous intracerebral haemorrhage in adults in their recommendations for the management of ICH related to coagulation and fibrinolysis. They suggested that the decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall state of the patient. In patients with a very high risk of thromboembolism (like patients with PHV in situ) in whom restarting warfarin is considered, warfarin therapy may be restarted at 7 to 10 days after the onset of the original ICH.

**CLINICAL BOTTOM LINE**

We conclude that anticoagulants, either heparin or OAC, can safely be withheld for a short period of up to 7–14 days in a patient with ICH on OAC with a very low probability of thromboembolic phenomenon and can safely be reinstated as early as 3 days for heparin and 7 days for OAC without major concerns of rebleeding. At the same time, there is a definite role for the rapid reversal of coagulopathy in acute settings using vitamin K, fresh frozen plasma or prothrombin concentrate.

**Conflict of interest:** none declared.

**REFERENCES**


eComment. Anticoagulation after intracranial haemorrhage in patients with a high risk of thrombosis

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We have read with great interest the article by Chandra and colleagues [1]. Anticoagulation in patients with warfarin-associated intracranial haemorrhage and a high risk of thrombosis and embolism are difficult questions in modern practice. It applies not only to patients with prosthetic heart valves, but also with venous thrombosis, atrial fibrillation, etc. The frequency of this complication is about 0.25–1.1% per year [2]. According to the study by Yung et al., the predictors of mortality in patients with warfarin-associated intracranial haemorrhage are the degree of initial anticoagulation (INR >3), greater stroke severity and intraventricular haemorrhage [2]. In other words, the amount and duration of bleeding depending on the capacity of the coagulation of blood determines the degree of the brain damage. So we need a rapid and careful recruitment of coagulation, which can be achieved by using the prothrombin complex concentrates. Vitamin K and fresh frozen plasma cannot fully satisfy these requirements. To reduce the