Intensive Care Med (2007) 33:1946–1953
DOI 10.1007/s00134-007-0765-1

ORIGINAL

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The headache over warfarin in British neurosurgical intensive care units: a national survey of current practice

Received: 8 February 2007
Accepted: 6 June 2007
Published online: 3 July 2007

These results were presented in part as a poster at the 19th Annual Congress of the European Society of Intensive Care Medicine in Barcelona, Spain, 24 September 2006.

Funding: none

E.O.T. was responsible for the concept and design of the study. R.A. and E.O.T. conducted the survey, analysed and interpreted the data and performed the literature search. R.A. drafted the article, which was then critically revised by E.O.T. R.A. and E.O.T. give final approval of the version to be submitted.

Dr E.O. Thomas acts as guarantor for this work and accepts full responsibility for the work and/or the conduct of the study, has access to all the original data, and controlled the decision to submit for publication. This work has not been published elsewhere.

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Abstract *Objective:* To ascertain current British practice regarding the emergency medical management of patients who sustain a spontaneous intracerebral haemorrhage (ICH) whilst receiving warfarin therapy and to compare this with established national and international guidelines. *Design:* Standardised, telephone based, questionnaire survey. *Setting:* All 32 adult British neuroscience intensive care units (ICUs) *Participants:* Duty consultant of each neuroscience ICU. *Results:* Response rate was 100%. The international normalised ratio (INR) would be reversed by over 90% of ICU consultants treating patients on warfarin with an ICH, except patients with mechanical heart valves (MHV), when only 59.4% would reverse. Prothrombin complex concentrate (PCC) was used by 15 ICUs (46.9%); however, only six units (18.8%) apply reversal strategies with PCC and intravenous vitamin K in accordance with national guidelines. Fresh frozen plasma (FFP) continues to be used by 71.9% of the ICUs. A protocol for warfarin reversal in ICH was present in five ICUs, of which four followed national guidelines. None of the units that use FFP had a protocol. Following ICH, two-thirds of the ICUs (65.6%) would commence bridging heparinisation in the first 4 days for MHV patients and 25% would recommence warfarin before, and 64.5% after, 7 days. *Conclusion:* There is considerable variation in practice amongst clinicians who regularly manage these patients and, in most cases (81.2%), practice is not in keeping with national or international guidelines. This study has demonstrated the need amongst senior ICU clinicians for a heightened awareness of current treatment recommendations and the availability of effective haemostatic therapies.

Keywords Intracranial haemorrhage · Anticoagulation · Clinical decision making · Intensive care · Evidence-based medicine

Introduction

Warfarin is an oral vitamin K antagonist used in the treatment and prevention of thromboembolic diseases [1–7]. Major haemorrhage secondary to long-term oral anticoagulation occurs in 1–5% of patients per annum [8]. This incidence increases with increasing patient age, duration of therapy, and intensity of anticoagulation [9]. The most feared haemorrhagic complication is spontaneous intracerebral haemorrhage. This occurs 8–10 times more

frequently than in non-anticoagulated patients, and more than doubles intracerebral haemorrhage-related mortality [10, 11]. There is an association between haematoma volume and the international normalised ratio (INR) at the time of bleeding [12]. Warfarin increases the risk of in-hospital haematoma expansion, and this expansion has been correlated with mortality [13, 14].

A recent phase IIb randomised controlled trial, in non-anticoagulated patients with intracerebral haemorrhage, revealed improved survival and functional outcome when haemostatic therapy was given within 4 h of bleeding [15, 16]. It has similarly been suggested that rapid reversal of the INR could limit haematoma expansion and improve outcome in warfarin-associated intracerebral haemorrhage [17].

The initial medical management of these patients should not present a therapeutic dilemma. The need to urgently reverse the coagulopathy and halt the intracranial bleeding outweighs the risk of thromboembolic consequences related to the underlying co-morbidity [18]. Recommendations for optimal anticoagulant reversal and its subsequent management exist [1, 2, 19–24]. The most recent guidelines from the British Committee for Standards in Haematology were updated in 2005 [2] and recommend that: "...reversal of anticoagulation in patients with major bleeding requires administration of factor concentrate in preference to FFP...(grade B, level III), and administration of intravenous rather than oral vitamin K (grade B, level IIa)." Equally, the European Society of Cardiology [7] recommends that in patients with mechanical heart valves: "... if the risk to life from continued bleeding is greater than that of valve thrombosis (e.g. intracranial bleeding) cessation of anticoagulation should be accompanied by prothrombin complex concentrate. Intravenous vitamin K may also be necessary if bleeding continues, as the half-life of factor VII is only 6 hours." They also state that: "...intracerebral haemorrhage always necessitates reversal of anticoagulation" [7].

All these recommendations, however, are published in specialist journals, and it is possible that clinicians managing patients with warfarin-associated intracerebral haemorrhage are not aware of the most recent published guidelines and not providing the best available evidence-based care. This was highlighted in a recent Italian study based in emergency departments, where only 6% of patients with oral anticoagulant-associated intracerebral haemorrhage received prothrombin complex concentrate [25].

We therefore decided to ascertain the current United Kingdom (UK) practice of consultants in neuroscience intensive care units regarding their initial and subsequent medical management of patients with warfarin-associated intracerebral haemorrhage. Provisional data from this study have previously been presented in abstract form [26].

Methods

A standardised questionnaire was constructed to enquire, in an open manner, about the usual management of a patient with a significant but non-fatal spontaneous intracerebral haemorrhage who was taking warfarin (Appendix). Five clinical scenarios were chosen to reflect the reasons for anticoagulation: which were (1) previous history of deep vein thrombosis (DVT) more than 6 months previously; (2) previous history of pulmonary embolism (PE) more than 1 year previously; (3) chronic stable atrial fibrillation (CSAF); (4) paroxysmal atrial fibrillation (PAF); (5) presence of metallic aortic or mitral valve (MHV). The questionnaire aimed to explore current practice regarding decisions for reversal of the oral anticoagulant effect, the products used for reversal, the use of intravenous heparin as bridging therapy, and whether and when oral anticoagulation would be restarted in each scenario.

All 32 adult neurosurgical units in the UK were identified from the Society of British Neurological Surgeons website (www.sbns.org). During one calendar month the duty consultant of the intensive care unit (ICU) that admits neurosurgical patients in each of these institutions was contacted by telephone. The nature of the study was explained to them and they were invited to contribute. Following completion of the questionnaire, verbal consent was obtained from all participating clinicians for anonymised results to be published.

Ethics approval was not deemed necessary, as this was a questionnaire survey of current practice.

Statistics

Results are presented as absolute values and ranges. Differences between groups were assessed with the chi-square test and a p value of ≤ 0.05 was considered statistically significant.

Results

The response rate was 100%. All 32 duty consultants contacted agreed to be part of this study. Half (16/32) of the ICUs were stand-alone neuro-intensive care units (NICU) with a mean of 6.3 (range 2–10) ventilated beds, and the other 16 units managed neurosurgical patients in general intensive care units (GICU) with a mean of 14.3 (range 9–21) ventilated beds. Fourteen (43.8%) of the consultants we spoke to had a lead role within their ICU.

Table 1 Usual product(s) the intensive care consultant uses/advises on his/her unit as optimal therapy for correcting coagulopathy in intracerebral haemorrhage patients

Agent	Number of positive responses $n = 32$ (%)	Use of factor VIIa (%)
IV vitamin K alone	1 (3.1)	
FFP alone	7 (21.9)	
FFP plus IV vitamin K	9 (28.1)	1 (3.1)
PCC alone	2 (6.2)	1 (3.1)
PCC plus IV vitamin K (recommendation)	6 (18.8)	1 (3.1)
PCC plus FFP	1 (3.1)	
PCC plus FFP plus IV vitamin K	6 (18.8)	

IV, intravenous; *FFP*, fresh frozen plasma; *PCC*, prothrombin complex concentrate

Table 2 Number of intensive care consultants that usually commence intravenous heparin, or therapeutic low molecular weight heparin, in the first 96 h post intracerebral haemorrhage, and the number who would recommence oral anticoagulants after the acute phase

Initial reason for OAC	Number that would commence bridging heparinisation in the first 96 h $n = 32$ (%)	Number that would restart OAC after acute phase $n = 32$ (%)
Previous DVT > 6 months	2 (6.2)	0
Previous PE > 1 year	3 (9.4)	3 (9.4)
CSAF	2 (6.2)	5 (15.6)
PAF	5 (15.6)	6 (18.8)
MHV	21 (65.6)	30 (93.8)
No heparin to any group	11 (34.4)	N/A
Restart OAC on advice only	N/A	2 (6.2)

OAC, oral anticoagulant; *DVT*, deep vein thrombosis; *PE*, pulmonary embolus; *CSAF*, chronic stable atrial fibrillation; *PAF*, paroxysmal atrial fibrillation; *MHV*, mechanical heart valve

Reversal decisions

Over 90% of consultants would reverse the INR to < 1.5 in intracerebral haemorrhage patients taking warfarin for DVT, PE, CSAF and PAF. However; 13 (40.6%) would not reverse the INR in patients with MHV. There were no differences between GICU and NICU consultants in reversal decisions.

Reversal strategy

Just under a half of ICU consultants (46.9%) would recommend the use of a prothrombin complex concentrate in one combination or other for the reversal of INR, and GICU consultants were twice as likely to use prothrombin complex concentrate as NICU consultants (10 vs. 5, $\chi^2 = 3.14$, $p = $ ns). Only six consultants (18.8%) would reverse with prothrombin complex concentrate and intravenous vitamin K as recommended by the national guidelines (2 GICU, 4 NICU). The majority of consultants (71.9%) use fresh frozen plasma (FFP) for warfarin reversal and three also use recombinant activated factor VII (Table 1).

In total, five (15.6%) units (2 GICU, 3 NICU) had an established protocol for the INR reversal of oral anticoagulant-associated intracerebral haemorrhage patients, and four of these recommended the use of intravenous vitamin K and prothrombin complex concentrate. None of the ICUs that use FFP had a protocol.

Bridging therapy and re-anticoagulation

Two thirds (65.6%) of consultants would commence therapeutic heparinisation in the first 4 days post intracerebral haemorrhage, mainly for MHV patients (Table 2). NICU consultants withheld bridging anticoagulation more often than consultants in GICU (7 vs. 4, $\chi^2 = 1.25$ $p = $ ns).

All GICU and the vast majority of NICU consultants would recommence warfarin in patients with MHV once the acute events have passed. Two NICU consultants said they would only restart warfarin in MHV patients on advice. No one would recommence warfarin in patients who

Table 3 Time following intracerebral haemorrhage when the intensive care consultant would usually restart oral anticoagulant

Time to restart warfarin	Total $n = 32$ (%)
Less than 2 days	0
2–4 days	2 (6.2)
4–7 days	6 (18.8)
7–14 days	8 (25)
After 14 days	12 (37.5)
Don't know/not my decision	4 (12.5)

had a DVT more than 6 months previously and less than 20% would do so for the other clinical scenarios described (Table 2).

A quarter of ICU consultants would recommence warfarin in the first 7 days post intracerebral haemorrhage; however, the majority (62.5%) would not restart warfarin until at least a week post haemorrhage (Table 3). Four consultants declined to answer as the decision was usually made post ICU discharge by another clinician.

Discussion

This is the first study we are aware of that specifically examines the current opinion and practice in the UK regarding anticoagulant reversal and its subsequent management in patients with intracerebral haemorrhage. It provides a snapshot of how consultants in neuroscience ICUs currently deal with these challenging patients. It is recognised that many of these patients will acutely present to the emergency departments of district general hospitals and this study did not address organisational issues regarding who decides to initiate haemostatic therapy or its timing. Personal experience, however, has revealed that advice is usually sought from the local tertiary neuroscience centre and we felt that auditing that advice could give a national perspective on this issue. In addition, these patients are usually admitted for continued management and optimisation to NICUs; this has been shown to improve outcome [27]. A 100% response rate makes this a comprehensive account of national practice, and it was designed to reflect the real-life dilemmas that occur in the management of these patients.

The first two questions of our study aimed to simulate a situation where a trainee might ring their intensive care consultant for advice as to the optimal initial management (warfarin reversal) of a patient with oral anticoagulant-associated intracerebral haemorrhage. The subsequent questions were aimed at exploring some of the more complex decisions regarding (re-)anticoagulation that occur following the acute event.

In these patients there is a short window of opportunity for warfarin reversal to influence the size of an evolving intracerebral haematoma. Time to treatment is the most important determinant of efficacy of warfarin reversal in the first 24 h [28, 29]. Warfarin inhibits the action of vitamin K within the liver as a cofactor in the production of factors II,VII, IX and X. Treatment options for reversing the coagulopathy include vitamin K, FFP, prothrombin complex concentrate and recombinant activated factor VII; these have been comprehensively reviewed recently [20, 28].

In the absence of randomised controlled trials, evidence-based guidelines have been published by national and expert bodies to assist non-specialists in their patients' management. Such guidelines exist for the reversal of warfarin effects in major haemorrhage [1, 2, 22–24]. All these published guidelines recommend intravenous vitamin K 5–10 mg and 25–50 U/kg of a prothrombin complex concentrate for the immediate reversal of the INR (Table 4). Prothrombin complex concentrate is recommended in preference to FFP as it is associated with a lower incidence of haematoma enlargement, corrects a prolonged INR more rapidly and is not associated with potential adverse transfusion-related reactions [2, 20, 28, 30, 31]. Additionally the traditional dose of 10 ml/kg of FFP is rarely effective and doses of up to 40 ml/kg may be necessary to reduce the INR below 1.5 [18]. This not only takes time to thaw and administer but also has the potential for volume overload in patients who are likely to have co-existing cardiovascular co-morbidities [20]. It is necessary to combine prothrombin complex concentrate treatment with intravenous vitamin K to prevent subsequent (12–24 h) rises in the INR due to the different half lives of warfarin and factor concentrate [32].

Despite these guidelines being available, this study has shown that considerable variation in reversal strategies amongst British ICU clinicians exists. Most units continue to use FFP either alone or in combination, and only six consultants (18.8%) recommended therapy in accordance with the above guidelines. It is noteworthy that four out of five ICUs who had a specific protocol concurred with these guidelines. This study, however, did not enquire about the treatment doses consultants would recommend, and the potential of under-dosing was not explored. It is interesting to note that GICU consultants were twice as likely as NICU consultants to use prothrombin complex concentrate. This may reflect their greater exposure to coagulopathic patients, and hence the product, in their non-neuroscience practice; whilst it did not reach statistical significance, this difference may be important clinically. This study was not designed to investigate how treatment decisions affected patient outcomes.

Of some concern is the off-licence use of recombinant activated factor VII (rFVIIa) by three consultants. Whilst there is evidence that this product normalises the INR in a small number of anticoagulated patients and volunteers, there is currently no prospective evidence to support its use in warfarin-associated intracerebral haemorrhage [18, 20, 33–35]. In fact, the recent phase IIb clinical trial demonstrated an increased incidence of arterial and venous thromboembolic events in the treatment arm of this study [16]. Since patients who suffer warfarin-associated intracerebral haemorrhage have independent risk factors for thromboembolism, this increased incidence may shift the risk–benefit ratio for this group of patients away from rFVIIa [36]. The results of the phase II pilot study currently being conducted in Italy may help address this issue (http://clinicaltrials.gov/ct/show/NCT00222625).

Table 4 Guidelines for reversal of anticoagulation in patients with warfarin-associated intracerebral haemorrhage

Institution	Year(s)	Recommendation
British Committee for Standards in Haematology [1, 2]	1998 & 2005	5–10 mg IV vitamin K plus 50 U/kg PCC in preference to FFP
Northern Regions Haematologists Group (UK) [22]	2004	5 mg IV vitamin K plus 30 U/kg PCC
Australasian Society of Thrombosis and Haemostasis [23]	2004	5–10 mg IV vitamin K plus 25–50 U/kg PCC and 150–300 ml FFP (NB: PCC licensed in Australasia in 2004 did not contain factor VII, hence the recommendation for additional FFP)
American College of Chest Physicians 6th Consensus Group [24]	2001	10 mg IV vitamin K plus PCC (dose not specified) (NB: PCC available in North America not licensed for warfarin reversal)

IV, intravenous; *FFP*, fresh frozen plasma; *PCC*, prothrombin complex concentrate

Unlike rFVIIa, which is prothrombotic, prothrombin complex concentrates merely normalise coagulation and the risks of thrombosis remain those of the underlying pathology [30, 32, 37].

In warfarin-associated intracerebral haemorrhage patients, the necessity to stop the bleeding outweighs all other considerations [18, 27]. Despite the statement previously quoted from the European Society of Cardiology [7], this study has shown that over 40% of consultants surveyed would not normalise the INR in patients with mechanical heart valves. The available literature, whilst retrospective in nature, supports the correction of the coagulopathy in all such patients [21, 34, 38–46].

Some studies have suggested that the careful introduction of intravenous heparin, or subcutaneous low-molecular-weight heparin, in patients with a high risk of thromboembolism is safe [42, 44]. Others state that the use of heparin as a bridging therapy should not be recommended [21]. If the risk of embolisation resulting in major stroke or death with a mechanical heart valve is 4% per year, and the risk of valve thrombosis is 1.8% per year, then the daily risk of valve thromboembolism has been estimated to be 0.016%, representing a 2-week risk of 0.2–0.4% [8, 18, 21]. Given the increased mortality and morbidity associated with early haematoma expansion, the literature would support withholding all forms of anticoagulation until the acute event has passed [14, 38, 39, 45]. Only 11 consultants (34.4%) in our study would not use heparin at all, and the majority (7/11) of these were NICU consultants.

There are no randomised controlled trials to guide practice on when to restart warfarin in patients who have suffered an intracerebral haemorrhage. In our study 25% of consultants would restart warfarin before 7 days and 62.5% from 7 days onwards. Data from retrospective studies suggests that withholding anticoagulants for at least 7 days is safe, even in patients with mechanical heart valves [42, 45]. The European Society of Cardiologists recommends anticoagulation should be withheld for 7 days and the European Stroke Initiative suggest 10–14 days [7, 18].

There have been no prospective studies determining the risk of recurrent intracerebral haemorrhage after restarting warfarin; however, small case series have shown a low risk of re-bleeding [38, 42]. Our survey of UK practice reveals that clinicians are uncertain when and in whom to restart oral anticoagulation. Whilst the decision was unanimous in the lowest- and highest-risk patients (DVT and MHV), there was considerable variation in practice in the less clear-cut indications. This probably reflects the need to consider these cases on an individual basis, and the decision analysis tree developed by Eckman and colleagues may provide guidance [47].

Conclusion

Patients who suffer warfarin-associated intracerebral haemorrhage are at high risk of dying or suffering severe disability. Time is brain, and there is an urgent need to provide optimal management for these patients in order to maximise functional outcome. There are currently no randomised controlled trials on which to base treatment, only national, international and societal expert guidelines. Our study has shown that the majority of neuroscience intensive care consultants do not manage patients in accordance with these guidelines and has demonstrated the need amongst senior ICU clinicians for a heightened awareness of current treatment recommendations and the availability of effective haemostatic therapies.

Appendix: Telephone survey of current practice in neurosurgical ICUs

Date

Unit Name/ Hospital

Tel:.....

Type: stand alone NICU // GICU with ring fenced NICU beds // GICU

Number of Level 3 beds (NICU.....) (GICU.....)

Consultant name

? Lead for NICU Y/N

? Lead GICU Y/N

Consent obtained Y/N

The following relate to the management of patients with significant but non-fatal spontaneous intracerebral haemorrhage who are taking oral anticoagulants:

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 INR? (say < 1.5) (tick all that apply)

a) Those with a previous history (more than 6 months) of DVT
b) Those with a previous history (more than 1 year) of PE
c) Those with chronic stable atrial fibrillation
d) Those with paroxysmal AF
e) Those with a metal aortic or mitral heart valve

What do you use/advise *on your unit* as optimal therapy for correcting the coagulopathy? (tick all, if any, that apply) (e. g. INR 3.2)

a) FFP
b) Vitamin K IV
c) Vitamin K PO
d) Prothrombin complex concentrate (PCC) e. g. Beriplex
e) Factor VIIa
f) Other.....

Does your unit have a protocol/policy for anticoagulation reversal in ICH? Y/ N

If Y how long for?.....

In which of the following patients, if any, would you *usually* commence intravenous heparin or therapeutic LMWH in the first 96 hours post ICH? (tick any that apply)

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

When, following ICH, would you restart oral anticoagulants?

a) Within 48 hours
b) Between 48 and 96 hours
c) Between 96 hours and 1 week
d) Between 1 and 2 weeks
e) After 2 weeks

In which of the following patients, if any, would you restart oral anticoagulation once the acute event has passed? (tick all that apply)

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

Thank you

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