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Intracranial Hemorrhage Secondary to Oral Anticoagulant Therapy: Insight into Pathogenesis, Prognosis and Management – A Review

Visweshwar H[1*] and Krithika Srikanthan[1]

Marshall University, Joan C. Edwards School of Medicine, Department of Internal Medicine, Huntington, West Virginia

[*]**Corresponding author:** Visweshwar H, Marshall University, Joan C. Edwards School of Medicine, Department of Internal Medicine, Huntington, West Virginia, Tel: 304-691-1086; E-mail: haresh.visweshwar@gmail.com

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Purpose of the review

Warfarin and the newer oral anticoagulants are efficacious in preventing stroke and pulmonary embolism in patients with atrial fibrillation and deep vein thrombosis. It remains a difficult therapeutic decision to use anti-thrombotic agents in elderly, where there is increased incidence of atrial fibrillation. Bleeding complications, especially life-threatening intracranial hemorrhage, are inevitable in this population because of increased incidence of falls. In this review, we analyze the incidence and prevalence of intracranial hemorrhage with warfarin and the newer oral anticoagulants

Recent developments

After nearly fifty years of warfarin use, newer oral anticoagulants are surpassing its use in the management of both arterial and venous thrombotic states. Though there has been this transition to newer anticoagulants, there is no ideal anticoagulant. Issues regarding predictors of hemorrhage, how to monitor anticoagulant therapy, early diagnosis and improving survival of patients with intracranial hemorrhage, still remain.

Summary

Although the use of newer anticoagulants is gaining momentum, because of the decreased incidence of intracranial hemorrhage, their use is still being debated in patients with underlying cancer, lupus anticoagulant state, metal valve prosthesis and pregnancy. We keenly await the results of multi-center trials to resolve this issue.

Keywords: Warfarin; Newer oral anticoagulants; Atrial fibrillation; DVT; Intracranial hemorrhage

Introduction

According to data from the National Electronic Injury Surveillance System (NEISS), warfarin is the most common drug-related cause of hospitalization (accounting for 33% of such hospitalizations) for adverse events among older adults in the United States [1]. Incidence of atrial fibrillation increases with age, with a prevalence of 0.1% in people over 55 years of age and 90% in those over than 80 years old. The number of patients with atrial fibrillation is likely to increase 2.5-fold during the next 50 years, reflecting the growing proportion of elderly individuals [2].

Incidence of intra-cerebral hemorrhage in patients receiving oral anticoagulants ranges from 0.3% to 1% per year [3]. About 50%-90% of intracranial hemorrhage (ICH) cases associated with warfarin use, occur while the INR is within the therapeutic range [4]. ICH has a 7- to 10-fold increased incidence with warfarin use, over patients not on oral anticoagulant therapy to an absolute rate of nearly 1%/yr for many stroke-prone patients [3]. The risk of warfarin-induced hemorrhage is particularly high when the INR exceeds four, as well as during the initial months of therapy [5]. However, Diamond et al found that the incidence of over-anticoagulation was only seen in 23% of patients developing subdural hematomas on warfarin therapy and there was no correlation between anticoagulant status and the extent of bleeding or prognosis [6].

Warfarin related ICH carries a particularly high risk of neurologic deterioration and death because of a high rate of hematoma expansion of about 50%. The risk of hematoma expansion is unknown with newer oral anticoagulants [7,8]. However, novel oral anticoagulants (NOACs)--apixaban, dabigatran, and rivaroxaban--have a significantly lower risk of intra-cerebral hemorrhage.

The relative risk (RR) reduction of stroke by oral anticoagu-

lant therapy is about 68% and the beneficial effect of anti-thrombotic therapy, far outweighs the risks of intra-cerebral bleeding in the elderly. Hence, age in itself is not considered acontraindication to treatment, and other risk factors are to be considered (Table 1) [9]. Serious bleeding, including warfarin induced ICH, is challenging and management includes rapid reversal of anticoagulation with hemostatic drug therapies, such as vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), recombinant factor VIIa (rFVIIa) or hemodialysis and idarucizumab with dabigatran. These therapies may not always be sufficient to stabilize the patient's clinical condition, and in the absence of randomized controlled trials, the preferred approach remains unclear and mortality remains high [10].

Predisposing factors:

Inherited	Acquired
Asian Ethnicity	Increasing Age
Black Ethnicity	Diastolic Hypertension
Presence of Apo-lipoprotein E2 allele	Alcohol Consumption
Decreased LDL	Decreased Platelet Count
Decreased TG	Hypo-albuminemia

Table 1: Predictors of ICH After Oral Anticoagulant Therapy.

Pharmacology of Oral Anticoagulants:

Warfarin blocks vitamin K dependent, gamma carboxylation of coagulation factors II, VII, IX and X. Dabigatran is a direct inhibitor of thrombin and rivaroxaban selectively inhibits factor Xa. The anticoagulant effect of warfarin is caused by a small fraction of the drug, since most (97%-99%) is protein bound (mainly to albumin), thus rendering it ineffective. Unlike the newer oral anticoagulants , the half-life of warfarin varies greatly among individuals, ranging from 35 to 45 hours (Table 2) [11]. Patients taking warfarin had a doubling in the rate of intra-cerebral hemorrhage mortality in a dose-dependent manner [12]. The hypothesis is that warfarin compromises the normal hemostatic mechanism of tissue factor interacting with activated factor VII to initiate the coagulation cascade [13]. Rivaroxaban is distributed heterogeneously to tissues and organs, and exhibits only moderate tissue affinity and does not substantially penetrate the blood-brain barrier. As thrombin has been implicated in microvessel injury during cerebral ischemia, dabigatran decreases the risk of intra-cerebral hemorrhage by direct inhibition of the thrombin-mediated increase in cerebral endothelial cell permeability. Dabigatran also does not increase the risk of secondary hemorrhage after thrombolysis, as seen in various rodent models of ischemia and re-perfusion [14]. The incidence of intracranial bleeding is apparently less with the newer oral anticoagulants when compared to warfarin [15].

	Warfarin	Dabigatran	Rivaraxaban	Apixaban
Mechanism	II, VII, IX, X	Thrombin	Factor Xa	Factor Xa
Dosing	Individual	150mg BID	20BID/10mg OD	2.5mg BID
Peak AC	3-5D	1-2H	2-4H	3H
Half Life	40H	17H	13H	12H
Antidote	Vit.K	None (PCC/ HD)	None (PCC/ VIIa)	None (PCC/ VIIa)
Renal Excretion	0%	80%	35%	25%
Drug Interaction	Multiple - Cyp2C9	PgpInh.	CYP3A4, Pgp	CYP3A4, Pgp

Table 2: Pharmacokinetics of Warfarin and Newer Oral Agents.

Drug interaction and oral anticoagulant therapy:

Warfarin is 99% plasma bound [16]. Alterations in cytochrome P450-mediated drug metabolism or disturbances in drug-protein binding lead to altered anticoagulant activity of warfarin. Interaction with drugs, releases unbound free molecule increasing bleeding tendency, which some think may lead to a paradigm shift in the management of anti-thrombotic therapy [17]. Compared to warfarin, dabigatran does not have CYP450 interaction, but it is a substrate of P-glycoprotein (P-gp) and therefore has drug interaction with rifampin, verapamil, carbamazepine, ketoconazole and dronedarone [18]. Rivaroxaban interacts with agents including erythromycin, clarithromycin, ritonavir and ketoconazole [18,19]. But unlike warfarin, dabigatran and rivaroxaban have no interaction with herbs and food, including food additives.

Duration of anticoagulation and ICH:

With the newer oral anticoagulants, the time interval between the duration of anticoagulation and the occurrence of internal hemorrhage is not available. With warfarin, 11% of the bleeds occurred within the first month, 20% within 2 months and 33% within 6 months. About 42% had been on anticoagulation for more than 3 years and majority of patients with subdural hematomas did not have a definite history of trauma [6]. Some studies found the highest incidence of ICH within the first 6 months (the duration of treatment for provoked first-time DVT/PE), but others found no relationship to the duration of anticoagulant therapy and incidence of ICH [20,21].

Trials of oral anticoagulant therapy and incidence of ICH:

The cumulative data from a meta-analysis of these trials revealed that the risk of ICH was about 50% less with NOACs (Table 3). When compared to warfarin, the reduction risk ratio was 0.44 (with 95% confidence interval) with both anti-thrombin and factor Xa inhibitor (RE-LY, ARISTOTLE, ROCKET& ENGAGE) trials. NOACs and LMWH had a similar incidence of internal hemorrhage. As expected, there was an increased risk of ICH with NOACs when compared with placebo (RR 3.31 with 95% confidence interval) [31]. Interestingly in one study, 150 mg of

dabigatran, twice a day, had an incidence of ICH of 0.1 per 100 patient years, while the incidence of dosing dabigatran 110 mg twice a day was 0.3 per 100 patient years [32]. All of the NOACs are qualitatively more effective than warfarin in significantly reducing ICH. But individually the magnitude of reduction in the risk of ICH varied among individual agents. However this does not prove that NOACs are far superior to warfarin, because in these trials comparing NOACs with warfarin, patients who had underlying cancer, lupus anticoagulant syndrome and patients with prosthetic cardiac metal valve were excluded. Also, in patients taking NOACs, there were case reports of increased GI bleeding, but a systematic review has found no evidence of increased GI bleeding with NOACs [33].

Study	Drug	No.	Indication	Rate-%/y
Lundstrom, 1989 [22]	Warfarin	213	A.Fib	0.5
European AF Trial, 1993 [23]	Warfarin	225	A.Fib	0
AFI 1994 [24]	Warfarin	1225	A.Fib	0.3
SPAF II 1995 [25]	Warfarin	550	A.Fib	0.9
Rocket Trial 2011 [26]	Rivaroxaban	7111	A.Fib	0.5
Engage Trial 2013 [27]	Edoxaban	7035	A.Fib	0.39
Re-Ly Trial 2009 [28]	Dabigatron	6015	A.Fib	0.3
Granger CB et al. 2011 [29]	Apixaban	9088	A.Fib	0.33
Connolly SJ et al. 2011 [30]	Apixaban	2088	A.Fib	0.4

Table 3: Intracranial Hemorrhage with Warfarin and Newer Oral Agents.

Management & Prevention:

Because of the high mortality involved with intracranial bleed, either from warfarin or the newer oral anticoagulants, it is prudent to attempt to avoid ICHs.

About one third of patients on oral anti-coagulant therapy have been started on the medication because of unproven benefit [6]. Avoiding drug interaction, patient education, drug compliance, caution with co-morbidities, discontinuing anticoagulant if appropriate, avoiding the use of alcohol and caution in patients with thrombocytopenia, is essential [34] and holding further anti-coagulation when patients develop sudden onset of severe headache is mandatory. Supra-therapeutic levels of oral anticoagulants in circulation can be avoided by prevention of drug- drug interactions, patient education, adequate therapeutic monitoring of INR with warfarin therapy, avoiding antithrombin/anti Xa inhibitors in severe renal failure, management of co-morbidities including severe diastolic hypertension and appropriate management of falls, especially in elderly individuals. Unfortunately in more than two thirds of patients, ICH occurs when the INR is within the therapeutic range [35,36].

Treatment:

In the management of warfarin-associated ICH, the administration of vitamin K alone is inadequate, as vitamin K does not reverse the hemostatic defect for many hours. Hemostatic levels of factor IX cannot be achieved, in most instances, by the conventional use of FFP in patients requiring reversal of warfarin [37]. In 2013, the FDA-approved prothrombin complex concentrate (PCC) for the urgent reversal of warfarin induced acute major bleeding. Rapid reversal of coagulopathy in geriatric patients on warfarin is pivotal to limit the extent of ICH. Larger volumes of FFP needed to reverse warfarin-induced coagulopathy are also associated with fluid retention and congestive heart failure in elderly patients. PCC on the other hand allows a more rapid reversal, as compared to standard treatment with only FFP and vitamin K [38].

In one non-randomized study, the time for warfarin reversal was significantly shorter with the use of PCC as compared to FFP (PCC-65 minutes and FFP-256 minutes, $P<0.05$) [39]. However, patients with a prior history of PE or DVT who receive three factor PCC for warfarin-associated ICH are 4.5 times more likely to sustain a VTE within 30 days [40]. In an observational study of patients with central nervous system bleeding, patients who received recombinant factor VII (rFVIIa), the time to INR normalization was approximately 2 hours [41]. In the absence of prospective, randomized data, recommendations regarding the reversal of warfarin-induced coagulopathy must rely on expert opinion [42-44]. No mortality benefit has been shown for one treatment regimen over another [45]. In the case of newer oral anticoagulants, the initial treatment is to hold further exposure to the agent and activated charcoal to prevent enteric absorption. With dabigatran, hemodialysis and the specific antibody idarucizumab appears to be very effective [46]. Direct and indirect factor Xa inhibitors have no specific FDA approved agent available to counteract their effect. The present management includes: holding further exposure to the agent, use of activated charcoal, administration of prothrombin complex concentrate and rFVIIa. The antidotes under trial for direct and indirect factor Xa include: andexanet alpha and ciraparantag. Andexanet alpha is a modified protein extracted from coagulation factor X, eliciting a significant, dose-dependent reduction in plasma anti-Xa activity [47]. Ciraparantag is a synthetic, small molecule antidote, binding to direct and indirect factor Xa inhibitors, including rivaroxaban, apixaban, edoxaban, enoxaparin and fondaparinux[48, 49]. Its mechanism of action for drug reversal includes binding to the drug and forming strong, non-covalent hydrogen bonds [50].

Recommencing oral anticoagulants after ICH:

There are no guidelines regarding oral anticoagulants following ICH. Patients have been recommenced on oral anticoagulant therapy for prosthetic heart valve following ICH and no life-threatening bleeding complications have been reported [51]. Following ICH, reinitiating anti-thrombotic therapy must be made

based on the relative risks versus benefits in individual patients, which will vary depending on the site of hemorrhage, continuing risk factors for further hemorrhage, and indication for anticoagulation [52]. Warfarin decreased the absolute rate of primary events by 0.7%per year (95% CI-0.4 to 1.7) and untreated atrial fibrillation was associated with risk of thromboembolism of 4.5% per year [53]. As re-bleeding is rare and the individuals have high a incidence of thromboembolic episodes without anticoagulant therapy, reinitiating therapy in patients with prosthetic metal valves is generally advised [54].

Risk of thrombosis after reversal of oral anticoagulant therapy:

The exact incidence of thromboembolic phenomena after stopping the incriminated anticoagulant and reversal of its effect is unknown [52], especially with the newer oral anticoagulants. In patients with prosthetic heart valves (PHV) the risk of thrombosis without anticoagulation may be as high as 22% per year [52]. In patients with atrial fibrillation, the risk of arterial thromboembolic episodes approaches 20%, especially when patients have additional risk factors. Interruption of oral anticoagulants for three to five days following a major bleed and for whom follow-up data were available, no further hemorrhages were recorded after a mean time of 2.8 years [55]. The thrombotic episodes following cessation of anti-thrombotic agents is mainly influenced by the underlying cause for initiation of thrombotic therapy including anti-phospholipid antibody syndrome, ball mitral valve versus aortic valve, associated vascular disease, underlying cardiac rhythm. However, overall duration of anticoagulant therapy and compliance with anticoagulant medication plays a role in determining whether thrombotic episodes will occur following cessation of therapy.

Prognosis:

The overall mortality rate for ICH secondary to anticoagulant use, ranges between 45%-60% [56]. About 70% of intracranial hemorrhage is intra-cerebral hemorrhage. The mortality rate is high in Asians, the elderly, and patients with higher diastolic blood pressure [57]. There appears to be no difference in the fatality rate following intracranial hemorrhage among patients receiving warfarin or other newer oral anticoagulant agents.

Discussion:

In the three major trials (Re-Ly -2009, Rocket -2011 and Engage trials -2013), the incidence of intra-cerebral hemorrhage was less with the newer oral anticoagulants when compared to warfarin. In patients who developed ICH, more than 50% were in the desired therapeutic range. About 70% of patients had intra-cerebral hemorrhages and the rest subdural hematomas. Subarachnoid hemorrhage occurred in a minority of patients. Major bleeding complications in these multi-center trials were, between 2.5%-3% but risk of intracranial bleeding was 50% lower with other newer oral anticoagulant agents than with warfarin [58]. However, these trials excluded patients that were pregnant, over the age of 80, had a diagnosis of cancer or lupus anticoagulant syndrome. Warfarin is still the drug of choice for patients with cancer, circulating anticoagulant, heparin-induced thrombocytopenia and valvular atrial fibrillation. As increasing age, the level of oral anticoagulant, genetic factors, high prevalence of concurrent cerebrovascular conditions, such as cerebral amyloid angiopathy or previous strokes, lower hemoglobin concentrations, renal dysfunction and low platelet count are independent predictors of intracranial hemorrhage; caution needs to be exerted when oral anticoagulant use is contemplated [59]. Obesity is independently associated with anticoagulation reversal failure [60]. Interestingly in J-RHYTHM study, concurrent use of aspirin and warfarin has not been shown to produce higher incidence of ICH (as patients may need dual therapy with atrial fibrillation and systemic arterial disease) [61]. The newer oral anticoagulants will most probably replace warfarin for treatment of atrial fibrillation and venous thromboembolism. Currently, outcomes of ICH with the antidotes for the newer oral agents are still unknown. Because of high morbidity and mortality, our aim should be to prevent ICH via the judicious use of oral anticoagulants and by maintaining a constant dialogue between the patient, provider and pharmacy teams.

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