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ORIGINAL ARTICLE

Bivalirudin as a Bridge for Anticoagulation in High Risk Neurosurgical Patients with Active DVT or High Risk of Thrombosis

Tariq Janjua · Eric Nussbaum · Jodi Lowary · Virginia Babbini

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Abstract
Background Bivalirudin is an ultrashort acting direct thrombin inhibitor, which has been used in place of heparin in selected settings. We describe our preliminary experience with the use of bivalirudin in patients who required anticoagulation for a deep vein thrombosis, prosthetic heart valve, or hypercoagulable state but were felt to be at high risk for the use of heparin.
Methods Eight patients in our neurocritical care unit required anticoagulation but were felt to be poor candidates for heparin either due to heparin-induced thrombocytopenia or due to high risk for intracranial hemorrhage. A standard protocol was utilized for bivalirudin with a loading dose of 0.75 mg/kg followed by a continuous infusion of 0.15 mg/kg hr. Serial aPTT levels were checked on a routine basis to monitor therapeutic effect. The bivalirudin infusion was continued for a period of 2 days to 2 weeks prior to starting coumadin therapy.
Results These patients were in the early postoperative period (within 48 h) following craniotomy, had suffered a recent large hemispheric infarct with hemorrhagic conversion, or had presented with an acute intracerebral hemorrhage. In this small series of patients, no intracranial hemorrhagic complications were encountered. No patients demonstrated progressive systemic thrombotic issues while on bivalirudin.
Conclusion Based on these findings, bivalirudin may represent a reasonable alternative in patients for whom heparin anticoagulation is contraindicated. A larger multicenter trial of bivalirudin in this setting may be appropriate

Keywords Direct thrombin inhibitors · Intracranial hemorrhage · Bivalirudin · Deep venous thrombosis · Prosthetic cardiac valve

Introduction

Prevention and treatment of deep venous thrombosis when a patient is at high risk for intracranial hemorrhage is a clinical challenge. The same is true with active intracranial hemorrhage or in the immediate postneurosurgical period. Once the decision is made to use anticoagulation in these patients, unfractionated heparin is usually the agent of choice. Fractionated heparin has a long half-life and therapeutic effectiveness is not measured. This can be risky in neurocritical care. The half-life of unfractionated heparin is close to 4 h and reversal requires active intervention. Intervention is done mostly after bleeding, which is too late for unstable circumstances. We propose short acting direct thrombin inhibition as a pathway for these high risk patients.

Methods

A retrospective review of data collected in a dedicated neurocritical care unit was conducted. Patients were selected from a list of patients who required direct thrombin agents from the clinical pharmacy database. All patients with use of bivalirudin were part of the original database. Patients who did not meet the basic criteria of a

For *BAN DVT* (Bivalirudin anticoagulation for neurosurgical patients with active DVT) Registry of National Brain Aneurysm Center, Saint Joseph's Hospital, Saint Paul.

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stay in the neurocritical care unit were excluded. Demographic information, original diagnosis, the indications to use direct thrombin inhibitors, and hospital outcome were included.

Results

Eight patients were included in the review. Demographics, diagnoses, and the total duration of use of bivalirudin are shown in Table 1. In these patients, the infusion was held for multiple reasons; the most common was redo cranial procedures including placement of new ventriculostomy catheter or permanent shunt placement. There was no neurocritical care unit mortality. There were neither intracranial nor systemic hemorrhagic complications. The range of aPTT to titrate bivalirudin was kept between 40 and 60 s. The initiation dose was based on the creatinine clearance (Table 2). The loading dose was part of the protocol although none of the patients received the loading dose. All patients were started on 0.15 mg/kg h infusion and titrated to achieve the desired goal of aPTT.

Representative Patients

Case 1

A 64-year-old female patient was admitted to the neurocritical care unit after being found down at home with intraventricular hemorrhage. She had a history of chronic obstructive pulmonary disease and mitral valve prosthesis 8 months prior to this admission. Her admission Glasgow coma scale was five with INR of three. She received emergent fresh frozen plasma with vitamin K. Her repeat CT-scan showed continued dilatation of the ventricles. A fiberoptic intracranial pressure probe was inserted with opening pressure of 35 cm H_2O. She was taken to the neurosurgical suite and clot evacuation was performed. Post-surgery she was kept in an induced coma with pentobarbital for the next 7 days. At the end of 7 days, due to her prosthetic valve and spontaneous intracranial hemorrhage, the decision was made to start bivalirudin infusion without bolus to keep aPTT between 40 and 60 s. She was converted to argatroban after 24 h due to a positive test for heparin-induced thrombocytopenia. She did not develop any complications from bivalirudin in the first 24 h. This was the first case where direct thrombin inhibition was used in this series.

Case 2

A 43-year-old male patient was found unresponsive in his bed. Initial resuscitation was performed by his wife, and he was brought to a regional hospital. He was transferred to our center with high grade subarachnoid hemorrhage. After an emergent diagnostic cerebral angiogram, he was taken to the operating room. A complex middle cerebral artery dissecting 1.5 cm aneurysm was treated. The procedure involved placement of ventriculostomy, left extracranial–intracranial bypass, and clipping of the aneurysm. The aneurysm was dissecting in nature, and occlusion was achieved due to flow reversal with extracranial–intracranial bypass. Postoperatively, he underwent neurocritical care unit management including early tracheostomy and gastrostomy placement. There was an episode of upper extremity deep venous thrombosis complicated with active pulmonary embolism. He was started on bivalirudin with a goal aPTT of 40–60 s. He was converted to warfarin after he tolerated bivalirudin without any complications. He was later discharged to acute care neurorehabilitation.

Table 1 Characteristics of patients and duration of bivalirudin

	Age	Sex	Diagnosis	Days of use
1	73	F	SAH, DVT with PE	28
2	43	M	SAH, ECIC Bypass, DVT with PE	10
3	58	F	SDH, MVR, L atrial thrombus	3
4	62	M	ICH, DVT	2
5	86	M	SDH, A. Fib with TIAs	2
6	41	F	SAH, Dural VT	15
7	28	M	SD Empyema, DVT with PE	2
9	63	F	ICH, MVR	2

Time above 48 h was not continuous infusion

SAH subarachnoid hemorrhage, *DVT* deep venous thrombosis, *PE* pulmonary embolism, *ECIC* extracranial–intracranial bypass, *MVR* mitral valve replacement, *ICH* intracranial hemorrhage, *TIAs* transient ischemic attacks, *SD* subdural

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Table 2 Bivalirudin initiation dose based upon creatinine clearance (CrCL)

CrCl (half time)	Starting dose (mg/kg h)
>60 (25 min)	0.15
30–60 (34 min)	0.08
<30 (57 min)	0.05

Case 3

An 86-year-old male patient came in after a fall with acute subdural hematoma. He was on warfarin for chronic atrial fibrillation. His INR was reversed with fresh frozen plasma and he was taken to emergent craniotomy for clot evacuation. After 1 week, he was started on a 24 h infusion of bivalirudin with a goal aPTT of 40–60 s. CT scan showed stable postsurgical changes. He was transitioned to unfractionated heparin infusion which was changed to warfarin within a few days. He was discharged to acute care rehabilitation.

Discussion

Direct thrombin inhibition is an established treatment for certain clinical conditions. There are two different types of direct thrombin inhibitors: bivalent and univalent. The bivalent inhibitors include agents like bivalirudin and lepirudin, while argatroban is a univalent agent. One of the recognized uses for direct thrombin inhibitors include heparin-induced thrombocytopenia, a condition where active thrombosis happens due to antibodies against heparin. It is an enigma to treat a patient who is at high risk for cranial bleed or has active bleeding with anticoagulation. Some of these patients present with intracranial bleeding per se from anticoagulation, most commonly warfarin. In these patients, the confounding factors include uncontrolled hypertension, traumatic brain injury, amyloid angiopathy, cerebral arteriovenous malformations, or cerebral aneurysms. In addition, these patients are bedbound for days and some have extensive neurologic damage. These are some of the most high risk patients for active thrombosis. If a prosthetic cardiac valve is in place, it can lead to high mortality and morbidity. As a neurocritical care challenge, these patients can be treated with a three phase clinical approach as shown in Table 3.

Table 3 Three phase approach to intracranial hemorrhage with active thrombosis or high risk of thrombosis

1. Management of the original bleed with risk of thrombosis
2. Management during the surgery or perioperative period
3. Postoperative period, after 24–28 h, with the original problem of risk of thrombosis or new active thrombosis

We used an ultrashort acting direct thrombin inhibitor with the above mentioned thought process. Bivalirudin at pharmacologic concentrations is an efficient inhibitor of thrombin generation, platelet activation, and clot formation [1]. It is a specific inhibitor of thrombin subtypes with high fibrinogen-procoagulant activities and its Arg-3-Pro-4 bond is slowly cleaved by these thrombin subtypes. This process acts as an 'on–off' switch of blood coagulation with a short reversible half-life (Fig. 1). Alpha thrombin is the central part of the prothrombin conversion. Beta and gamma are a less active part. Neutrophil elastase and cathepsin-G cleave the B-chain into epsilon and zeta. Zeta is the active form with similar activity as alpha. Both alpha and zeta thrombin, which have high fibrinogen-clotting activities, are inhibited [2]. Another aspect is the antiplatelet activity. It is not an antiplatelet agent although it suppresses thrombin-dependent platelet activation. This is achieved via inhibition of PAR-1 cleavage. It also inhibits collagen-induced platelet procoagulant activity as well as systemic thrombin levels in patients undergoing active coronary intervention [3]. The third action is to inhibit fibrin-bound thrombin by displacing fibrin from its binding site. Bivalirudin is not inhibited by platelet factor 4 which is released from activated platelets and binds with high affinity to heparin, thereby abrogating its activity. The fourth action is to impair vascular nitric oxide bioavailability in vitro as well as in vivo. The suggested possible mechanism is facilitation of vascular sequestration of myeloperoxidases. This might be related to lower bleeding in studies where comparison is done to heparin [4].

One of the key reasons to use this agent for high risk neurocritical care patients is the half-life. In one Chinese study in healthy subjects, the half-life was 33 min [5]. This short half-life helps with reversal without any active interventions. One case report of use of bivalirudin for coronary stent placement with an active intracranial hemorrhage showed no increase in bleed size [6]. Neuroendovascular interventions require antiplatelet and/or antithrombotic agents. One study of 30 patients reported safe use of bivalirudin without intracranial hemorrhage [7]. In experimental studies in an animal model, the combination with recombinant tissue plasminogen activator did show conversion to hemorrhage [8, 9].

Renal function is one of the key factors for clearing the agent, and the half-life is based upon creatinine clearance (Table 2) which is 20–25 min with a normal creatinine clearance. Due to the ultrashort life, the reversal for this agent may not be needed except in low creatinine clearance where the duration is prolonged. The effectiveness is measured with aPTT or thromboelastometry. Thromboelastometry was used in a cardiac patient with heparin-induced thrombocytopenia to monitor bivalirudin dosage. The onset of fibrin polymerization was delayed with

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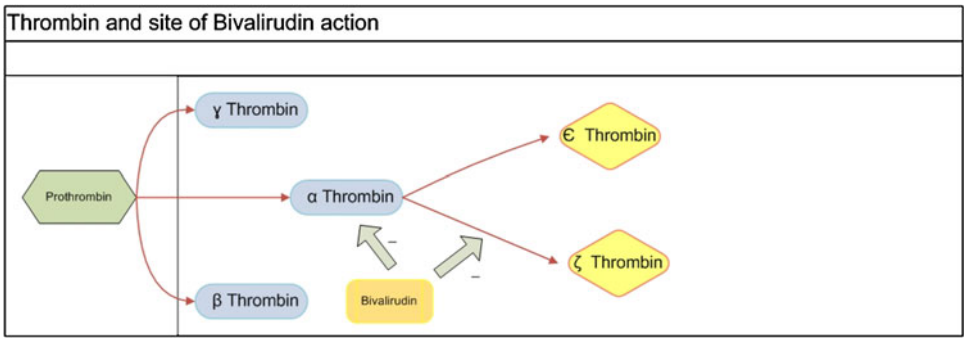

Fig. 1 Thrombin inhibition by direct thrombin inhibitor bivalirudin

argatroban, although the maximal clot formation reached the same level over time [10]. Reversal may also be possible with procoagulant factors. Recombinant activated factor VII used ex vivo has shown to reverse the effect of bivalirudin on aPTT. This effect was tested with thromboelastometry [11]. Activated clotting time can also be used although thromboelastometry is superior to activated clotting time to adjust bivalirudin dosage [12]. Like other direct thrombin inhibitors, it will prolong PT duration and INR, although less as compared to argatroban [13]. There is evidence that renal failure patients are the exception to the use of this agent due to bleeding complications with creatinine clearance <60 ml/min having significantly increased risk [14]. The last element to consider in the use of this agent is the cost analysis. Heparin with glycoprotein IIb/IIIa inhibitor versus bivalirudin was compared for cost in the ACUITY trial. Higher acquisition costs for bivalirudin were partially offset by lower hospitalization and bleeding complications [15].

Anticoagulation in very high risk neurocritical care patients is always a neurosurgical and neurocritical care enigma. This series is not controlled, and a retrospective review was done on an uncontrolled dataset. To perform a controlled prospective study of direct thrombin inhibitors in this population would be expensive, and the challenge of recruitment may be difficult. The authors propose a national registry, where the data are collected prospectively in involved centers. This registry may help to create an organized pathway for use of direct thrombin inhibitors. A limitation of the current paper is the type of patients included in this series. Patients with and without cranial procedures are included, and there are patients with prosthetic valves. Another limitation is that in some patients, a preventive approach was used and in others a therapeutic approach. In a large series or a registry, this will be more evenly divided and would show more clarity.

Conclusion

In this small series, the use of direct thrombin inhibition in neurosurgical patients seems to be safe with minimal side effects. No serious bleeding complications were seen. The protocol used was simple, although time intensive due to the utility of a dedicated neurocritical care unit. The limitations can be overcome with a broader registry or a multicenter prospective trial in these patients.

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