Anticoagulation for the prevention of central venous catheter associated-thrombosis: an evidence based commentary

Leki przeciwkrzepliwe w zapobieganiu zakrzepicy związanej z cewnikowaniem w żyłach centralnych – komentarz oparty na danych naukowych

Menaka Pai, Mark A. Crowther
McMaster University, Hamilton, ON, Canada

Central venous catheters (CVC) have become critical to the management of patients with malignancy as they allow convenient long-term access to the venous system. This facilitates the intravenous administration of antibiotics, analgesics, blood products and chemotherapeutic agents, including vesicants that cannot be safely given via peripheral veins. Furthermore, central venous catheters allow administration of total parenteral nutrition to patients who cannot tolerate oral intake due to the toxic effect of chemotherapy on the gastrointestinal mucosa. They also assist in the frequent blood sampling required to monitor patients on chemotherapy. Maintenance of patency of central venous catheters is therefore critical to the delivery of effective cancer care.

Catheter failure can be due to many different causes including structural failure, infection, malposition (for example migration of the catheter tip out of the central circulation into a peripheral vein) and thrombosis [1]. While all causes of catheter failure can be indirectly life-threatening, as they prevent the timely delivery of chemotherapy and supportive care, catheter associated thrombosis may, rarely, pose a direct threat to life. There are two forms of catheter associated thrombosis. Small clots or fibrin sheaths can form around a catheter preventing aspiration and/or infusion but not impacting the central venous circulation. Larger clots can also develop in the setting of catheters, obstructing flow within the deep venous system and producing signs and symptoms of deep vein thrombosis (such as arm, head or neck swelling). This may rarely lead to pulmonary embolism [2]. Severe cases with clot extension into the central circulation may be associated with superior vena cava syndrome as well. Central venous catheters placed in the femoral veins are an independent risk factor for deep vein thrombosis (DVT) of the leg [3].

Research on the prevention of central venous catheter associated thrombosis initially studied the impact of low doses of warfarin. Although suggesting that fixed-dose warfarin reduce the risk of thrombotic failure, these studies enrolled only small numbers of highly selected patients. As a result, fixed-dose warfarin for prevention of catheter thrombosis was not widely adopted. Subsequently, heparin and low molecular weight heparin preparations have been evaluated for the primary prevention of catheter associated thrombosis. Unfortunately, as documented in the systematic review published by Akl et al. [4], these studies have failed to demonstrate that antithrombotic agents consistently reduce the risk of clinical thromboembolism or other potential complications such as death.

Recent studies have been performed by research groups well positioned to undertake methodologically rigorous studies powered to detect important differences. These studies have been largely negative. In examining why they failed to observe a clinically important reduction in thrombosis, it is important to identify the predicted and actual risk of thrombosis in the placebo or control arm of these studies; when compared to both historical rates of thrombosis, and the clinical perception of the risk of thrombosis, the actual rate of development of symptomatic thrombi has been very low in these studies [5]. As a result, studies have been underpowered to detect a true reduction in the rate of catheter associated thrombosis, if such reduction in fact exists.

On this background, the systematic review published by Akl et al. deserves careful appraisal. This comprehensive review of the published literature sought to evaluate the efficacy and safety of anticoagulation in reducing venous thromboembolic events in cancer patients with CVCs. In total, 9 randomized controlled trials were included in the meta-analysis. Heparins did not reduce symptomatic DVT (relative risk [RR] 0.43, 95% CI 0.18–1.06), mortality (RR 0.74, 95% CI 0.40–1.36), infection (RR 0.91, 95% CI 0.36–2.28), major bleeding (RR 0.68, 95% CI 0.10–4.78) or thrombocytope-

Correspondence to:
Mark A. Crowther, MD, MSc, FRCP(C), Professor and Chair, Division of Hematology, St. Joseph's Hospital, McMaster University, Room L208, 50 Charlton Ave. East, Hmilton, ON, L8N 4A6, Canada, phone: 905-521-6024, fax: 905-540-6568, e-mail: crowthrm@mcmaster.ca
Received: November 6, 2007. **Accepted in final form:** December 6, 2007.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2007; 117 (11-12): 494-496

nia (RR 0.85, 95% CI 0.49–1.46). Similarly, warfarin did not produce a reduction in symptomatic DVT (RR 0.62, 95% CI 0.30–1.27). However, when studies assessing different types of anticoagulants were pooled, symptomatic DVT rates were significantly reduced (RR 0.56, 95% CI 0.34–0.92).

This ultimate finding, that when their effects are pooled anticoagulants reduce the risk of symptomatic DVT, is difficult to interpret and impossible to implement in clinical practice. The pooled intervention is a heterogeneous "grab bag" of interventions, ranging from fixed dose unmonitored warfarin, to prophylactic dose low molecular heparin, to more intense warfarin therapy requiring international normalized ratio monitoring. These interventions are so dissimilar, that the results of this analysis cannot be translated into a single strategy that can guide clinical practice.

The seminal conclusion from this systematic review is that there is no evidence that any particular intervention reduces the rate of clinically important central venous catheter associated thrombosis in either a statistically or clinically important fashion. As a result, such therapy cannot be recommended. These conclusions are supported by another recent meta-analysis which confirmed that anticoagulation does not significantly reduce symptomatic venous thromboembolism in any patient population (including patients with malignancy) [6].

Although not specifically considered by the authors, there are dangers associated with the use of anticoagulants in patients with cancer and central venous catheters. The most important risk is bleeding. The subjects in these studies had a mean age less than 60, and many had a minimum life expectancy greater than three months. These carefully selected patients could be considered to be at a low risk for adverse events when exposed to anticoagulants. When extrapolated into the "real world" it is very likely that patients at high or very high risk of hemorrhage would be exposed to the intervention of interest. Although the systematic review failed to demonstrate an increase in major bleeding it is possible that such bleeding would occur when an unselected group of patients is exposed to anticoagulants in an effort to prevent CVC associated thrombosis.

Where should we go from here? This review reinforces that there is no evidence to support the use of anticoagulation for the primary prevention of CVC associated thrombosis. Whether anticoagulants are effective for secondary prevention of thromboembolism cannot be ascertained from this review nor does this review speak to the issue of treatment of line-associated clots. Interestingly, a recent study suggests that therapeutic dose anticoagulation may allow ongoing use of a catheter which would otherwise require removal [7].

If additional studies are to be performed in this area their sample size calculations should be based upon the rates of thromboembolism observed in the placebo arm of contemporary studies [4]. This will give them the power to detect clinically important reductions in the rate of thrombosis. Studies must also acknowledge the heterogeneous nature of cancer patients – a group with diverse comorbidities, concurrent therapies, bleeding risks, and underlying disease. Given the potential for anticoagulant interventions to cause bleeding in unselected patients with malignancy, study populations should aim to reflect this diversity and should include the largest possible population of patients, including those identified to be at high risk of either thrombocytopenia or bleeding.

REFERENCES

1. Bishop L, Dougherty L, Bodenham A, et al. Guidelines on the insertion and management of central venous access devices in adults. Int J Lab Hematol. 2007; 29: 261-278.
2. Ascher E, Salles-Cunha S, Hingorani A. Morbidity and mortality associated with internal jugular vein thromboses. Vasc Endovasc Surg. 2005; 39: 335-339.

From the Editor

Synopsis: Akl EA, Karmath G, Yosuico V, et al. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Cochrane Database Syst Rev. 2007; 3: CD006468.

In this systsmatic reviews with meta-analysis of 9 randomised controlled trials the authors assessed the efficacy of anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Together 2216 patients were included in the analysis. The use of low molecular weight heparin (LMWH) or unfractionated heparin compared to no anticoagulation was associated with similar risk of death (RR 0.74), symptomatic deep vein thrombosis (DVT; RR 0.43), asymptomatic DVT, thrombocytopenia, infection and major bleeding (RR 0.68); similar effect was observed in the analysis including only LMWH. Warfarin had no effect on the risk of symptomatic DVT in comparison with no anticoagulation (RR 0.62). The effect of warfarin was similar to nadroparin in respect of risk of death at 90 days and 6 months (RR 0.48), central venous catheter removal, venous thromboembolism at 90 days (RR 0.75), bleeding (RR 0.32) and thrombocytopenia. The use of any anticoagulation (heparin or warfarin) in comparison with no anticoagulation was associated with significantly lower risk of symptomatic DVT (RR 0.56), similar risk of death, asymptomatic DVT, thrombocytopenia, infection and major bleeding.

Prepared by: Małgorzata Bała, MD, PhD

3. Merrer J, de Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA. 2001; 286: 700-707.
4. Akl EA, Karmath G, Yosuico V, et al. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Cochrane Database Syst Rev. 2007; 3: CD006468.
5. Couban S, Goodyear M, Burnell M, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol. 2005; 23: 4063-4069.
6. Kirkpatrick A, Rathbun S, Whitsett T, Raskob G. Prevention of central venous catheter-associated thrombosis: a meta-analysis. Am J Med. 2007; 120: 901.e1-901.e13.
7. Kovacs MJ, Kahn SR, Rodger M, et al. A pilot study of central venous catheter survival in cancer patients using low-molecular-weight heparin (dalteparin) and warfarin without catheter removal for the treatment of upper extremity deep vein thrombosis (The Catheter Study). J Thromb Haemost. 2007; 5: 1650-1653.

KOMUNIKAT

Sekcja Reumatologiczna Towarzystwa Internistów Polskich
Sekcja Medycyny Rodzinnej
Polskiego Towarzystwa Reumatologicznego
Katedra i Klinika Reumatologiczno-Rehabilitacyjna
i Chorób Wewnętrznych Uniwersytetu Medycznego
im. Karola Marcinkowskiego w Poznaniu

zawiadamia, że

Ogólnopolska Konferencja
„Choroby reumatyczne w praktyce internistycznej"

odbędzie się
w Poznaniu 11–12 kwietnia 2008 roku

Tematy

1. Choroby reumatyczne w wieku podeszłym: fizjopatologia wieku podeszłego, najczęstsze problemy kliniczne, leczenie farmakologiczne
2. Zespół antyfosfolipidowy. Problemy związane z hematologią, położnictwem, transplantologią

Oprócz wykładów przewidziana jest prezentacja prac oryginalnych.

Przewodniczący Komitetu Organizacyjnego
prof. dr hab. med. Irena Zimmermann-Górska

Komitet Organizacyjny
Katedra i Klinika Reumatologiczno-Rehabilitacyjna
i Chorób Wewnętrznych Uniwersytetu Medycznego
im. Karola Marcinkowskiego
ul. 28 Czerwca 1956 r. 135/147, 61-545 Poznań
tel.: 061-831-03-17, 833-28-11, fax: 061-831-03-17
e-mail: zimmermanngorska@hotmail.com;
puszczewicz@hotmail.com