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New Guidelines for Antithrombotic Therapy: Making Blood Thinner Than Water

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Prevention of venous thromboembolism remains a crucial component of patient care following major surgery. Although neuraxial anesthesia and analgesia reduce the risk of venous thrombosis, a significant risk remains, even in the presence of a continuous epidural infusion containing a local anesthetic.[1] As a result, pharmacologic (and/or mechanical) prophylaxis is warranted. Thromboprophylaxis is based upon identification of risk factors. The risk factors for thromboembolism include trauma, immobility/paresis, malignancy, previous thromboembolism, increasing age (over 40 years), pregnancy, estrogen therapy, obesity, smoking history, varicose veins and inherited or congenital thrombophilia. Not surprisingly, only the healthiest patients undergoing minor surgery are not considered candidates for thromboprophylaxis postoperatively.

Guidelines for antithrombotic therapy, including appropriate pharmacologic agent, degree of anticoagulation desired and duration of therapy, continue to evolve. Recommendations by the American College of Chest Physicians (ACCP) are based upon prospective, randomized studies that assess the efficacy of therapy using contrast venography or ultrasonography to diagnose asymptomatic thrombi. Clinical outcomes such as fatal pulmonary embolism (PE) and symptomatic deep venous thrombosis (DVT) are not primary endpoints.

Since the first Conference on Antithrombotic Therapy in 1986, ACCP recommendations have included progressively higher levels and longer durations of thromboprophylaxis.[2,3] Despite the successful reduction of asymptomatic thromboembolic events with routine use of antithrombotic therapy, an actual reduction of clinically relevant events has been more difficult to demonstrate.[4,5]

In September 2004, ACCP released the proceedings of the Seventh Conference on Antithrombotic and Thrombolytic Therapy[3] **[see Table 1]**. These recommendations represent new challenges in the management of patients undergoing neuraxial (and invasive/noncompressible peripheral) blockade. Specifically:

• High-risk general surgery patients (i.e., those greater than 40 years of age undergoing a major procedure) are recommended to receive unfractionated heparin subcutaneously (SC) every *eight* hours. There are no data documenting the safety of neuraxial catheters with this dosing regimen.[6] Indeed it is likely that a significant number of patients will be therapeutically anticoagulated for a brief time. Furthermore the dosing schedule hinders catheter removal during a trough in anticoagulant activity.

• Fondaparinux is now recommended as an antithrombotic agent following major orthopedic surgery. The extended half-life (approximately 20 hours) allows once-daily dosing, which also impedes safe catheter removal. Both the American Society of

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Regional Anesthesia and Pain Medicine (ASRA) and ACCP recommend against the use of fondaparinux in the presence of an indwelling epidural catheter.[3,6]

• The target international normalized ratio (INR) for warfarin therapy following total joint replacement is 2.5 (range 2.0-3.0). This is considerably higher than the level achieved by many orthopedists, and if adapted, would necessitate earlier removal (or avoidance) of epidural catheters.

• There is a trend toward initiating thromboprophylaxis in close proximity to surgery. Early postoperative (and intraoperative) dosing of low molecular weight heparin (LMWH) was associated with an increased risk of neuraxial bleeding.

• The duration of prophylaxis has been extended to a minimum of 10 days following total joint replacement or hip fracture surgery. The recommended duration for hip procedures is 28-35 days. It has been demonstrated that the risk of bleeding complications is increased with the duration of anticoagulant therapy. The interaction of prolonged thromboprophylaxis and previous neuraxial instrumentation, including difficult or traumatic needle insertion, is unknown.

ACCP recommendations on antithrombotic therapy are periodically revised. Likewise ASRA consensus statements on neuraxial anesthesia and anticoagulation also are subject to timely revision as justified by evolution of information and practice. A recent publication on serious neurologic complications in Sweden between 1990 and 1999 warrants consideration regarding previous recommendations regarding the safety of once-daily LMWH in the presence of an indwelling epidural catheter. The series by Moen et al.[7] included 1,260,000 spinal and 450,000 epidural blocks performed over a decade. Among the 33 spinal hematomas, 24 occurred in females, 25 were associated with epidural anesthesia and a coagulopathy (existing or acquired) was present in 11 patients; two of these patients were parturients with hemolysis-elevated liver enzymes and low platetets (HELLP syndrome). The time interval between needle/catheter placement, operating room catheter removal and neurologic symptoms varied from six hours to 14 days (median 24 hours). The presenting complaint was most often lower-extremity weakness. Only five of 33 patients recovered neurologically (due to delay in the diagnosis/intervention). While these demographics, risk factors and outcomes confirm those of previous series, there are several new (and disturbing) results that require discussion:

• Four patients with indwelling epidural catheters had received 5,000 U unfractionated heparin during a vascular procedure, supporting the findings of the ASA Closed Claims Project.[8] The continued occurrence of spinal hematomas among this patient population emphasizes the need for vigilance in neurologic monitoring.

• The methodology allowed for calculation of frequency of spinal hematoma among patient populations. Parturients undergoing epidural analgesia for labor and delivery experienced a one-in-200,000 risk of spinal hematoma. For women undergoing total knee replacement (under epidural blockade), however, the risk was one in 3,600. These occurrences document the differences associated with age (including spinal canal pathology), thromboprophylaxis and duration of neuraxial catheterization.

• One-third of all spinal hematomas occurred in patients receiving thromboprophylaxis *in accordance* with the current guidelines for neuraxial anesthesia and anticoagulation (needle

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placement 10 hours after LMWH and LMWH administered two hours after catheter removal).

• Once-daily dosing of LMWH is the primary mode of thromboprophylaxis following total joint replacement in Sweden. The one-in-3,600 risk of spinal hematoma for women undergoing total knee replacement is similar to that calculated for the *twice-daily* dosing LMWH regimen in North America. This suggests that the European LMWH dosing schedule may not be as safe as previously considered.

In summary anesthesiologists are urged to maintain current knowledge of their institutional protocols for thromboprophylaxis. Changes may have been implemented based on the 2004 ACCP update. Likewise it is likely that the information contained in the series by Moen et al.[7] will result in a re-examination of both the North American and European LMWH guidelines. Importantly, since spinal hematoma may occur even in the absence of identifiable risk factors, neurologic monitoring is critical to allow early evaluation of neurologic dysfunction and prompt intervention. We must focus not only on the prevention of spinal hematoma but also optimization of neurologic outcome.

Table 1: Pharmacological Venous Thromboembolism Prophylaxis and Treatment Regimens

Total Hip or Knee Arthroplasty and Hip Fracture Surgery

- Fondaparinux ..... 2.5 mg SC qd started 6-8 h after surgery
- LMWH* ..... 5,000 U SC qd started 12 h before surgery, or 2,500 U SC 4-6 given hours after surgery, then 5,000 U SC daily
- Warfarin ..... Started the night before or immediately after surgery and adjusted to prolong the INR=2.0-3.0

Minor General Surgery, Spine, Vascular and Arthroscopic Procedures (with NO additional risk factors present)†

- Early mobilization
- No pharmacologic thromboprophylaxis

Minor General Surgery , Vascular or Spine Surgery (with additional risk factors present) and Major General or Gynecologic Surgery (with NO additional risk factors present)

- Unfractionated heparin ... 5,000 U SC q 12 hours, started 2 hours before surgery
- LMWH ..... 3,400 U SC qd, started 1-2 hours before surgery

Major General or Gynecologic Surgery and Open Urologic Procedures (with additional risk factors present)

- Unfractionated heparin ... 5,000 U SC q 8 hours, started 2 hours before surgery
- LMWH ..... >3400 U SC qd, started 1-2 hours before surgery

SC = subcutaneous; LMWH = low molecular weight heparin; INR = international normalized ratio.

** LMWH formulations available in North America are enoxaparin and dalteparin.*

†The risk factors for thromboembolism include trauma, immobility/paresis, malignancy, previous thromboembolism, increasing age (over 40 years), pregnancy, estrogen therapy, obesity, smoking history, varicose veins and inherited or congenital thrombophilia.

Based on recommendations from reference number 3 in article text.

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