Title: Efficacy of Low-dose Intravenous Heparin in Prevention of Thromboembolism in the SICU

Funding: Foundation for Anesthesiology Education and Research Resident Fellowship Grant (Mentee: Sara Chang, Resident; Mentor Paul Wischmeyer M.D.)

Principle Investigators: Sara S. Cheng, MD,PhD; Paul Wischmeyer, MD; Nathan Pearlman, MD

Brief protocol summary:
This a randomized, prospective, single-blinded pilot study for demonstration of safety and feasibility of study design, and estimation of primary outcome event frequency. The study population is adult patients who were admitted to the SICU after major surgery. Patients are randomized to subcutaneous heparin or intravenous heparin, which is titrated to a goal PTT range of 40-45. The primary endpoint is lower extremity DVT. DVT detection is via screening lower extremity Doppler ultrasounds obtained on days 0, 5, and 10. These are being performed by Kristen Nordenholz, MD and David Matero, MD, from the Division of Emergency Medicine. Daily blood samples are being drawn for analysis of coagulation parameters, inflammatory and coagulation biomarkers. Secondary endpoints including 28 day mortality, renal failure, ventilatory failure, and pulmonary embolism are being recorded for 28 days. 6 month mortality will also be recorded. This study is being funded by a grant awarded to Sara Cheng, MD, by the Foundation for Anesthesia Education and Research.

Enrollment:
Candidates for enrollment are identified by research coordinator Angela Baer, RN. She conducts prospective screening of general surgery clinic patients and enrolls them during their pre-operative appointment if possible. Enrollment began in September of 2008. 13 patients been successfully enrolled. 7 were randomized to subcutaneous heparin, while 6 were randomized to intravenous heparin.

Primary endpoint: Lower extremity DVT
Of 13 patients, one patient had a large proximal lower extremity clot on day 0 screening ultrasound. A formal ultrasound was ordered, which confirmed the diagnosis. The patient had an IVC filter placed and his anticoagulation managed according to standard of care. 1 patient died on post-operative day 6 of an acute event that was deemed to have very low likelihood of relationship to study drug. Of the remaining 11 patients, all 11 received day 5 ultrasounds and 7 received day 10 ultrasounds. All patients that were still in the hospital received study ultrasounds in a timely fashion by our ED collaborators.

Laboratory data:
Christine Hamiel in Dr. Wischmeyer’s laboratory has been analyzing daily blood samples for 7 days post-operatively a device called the Sonoclot, which provides data on coagulation that is very similar in type to the thromboelastogram, or TEG. The average ACT of patients receiving IV heparin was identical to that of normal volunteers, while the ACT of patients receiving subcutaneous heparin was markedly decreased when compared to the other two groups. Clot rate is a Sonoclot parameter that is roughly analogous to thrombin burst rate; the higher the number, the more rapid or robust the thrombin burst. Clot rate in patients receiving subcutaneous heparin was markedly increased, whereas patients receiving IV heparin had clot rates similar to non-operated controls.

These preliminary results are exciting for several reasons. First, the administration of intravenous heparin using the PTT as a target is validated by these data. Targetting the PTT gives us a reproducible change in the ACT and clot rate. The standard deviation on these data is quite small after only 10 patients. Secondly, the data suggests that this population of post-surgical patients
are actually hypercoagulable, and that administration of subcutaneous heparin is not enough to normal their coagulation. Thirdly, it suggests that administration of low-dose intravenous heparin, while mildly elevating the PTT, does not increase the activated clotting and does provide correct the hypercoagulable state that subq heparin does not effect. This may be important data for surgeons hesitant to administer intravenous heparin to surgical patients, for fear of bleeding complications.

Future directions:
As of May 19th, 2009, 22 patients have been enrolled. We anticipate enrolling 50-70 total patients by the end of 2009. Poster presentations of this data are already being prepared for presentation at the International Society of Thrombosis and Haemostasis, Western Anesthesiology Resident Conference, and Shock Society. We will begin ELISA analysis of serum samples in spring 2009 for a range of inflammatory mediators and coagulation markers. Proteins of interest include IL-6 and activated protein C.