Phoebe Kaiser
Dr. med.

Coagulation parameters and heparin-induced IgG antibodies in patients after lower limb trauma requiring immobilization treated with low-molecular-weight heparin, reviparin – a laboratory study of a placebo controlled clinical trial

Geboren am 11.11.1975 in Mannheim
Reifeprüfung am 21.06.1994 in Mannheim
Studiengang der Fachrichtung Medizin vom WS 1994/95 bis WS 2001/02
Physikum am 19.03.1997 an der Universität Heidelberg
Klinisches Studium in Mannheim
Praktisches Jahr in Heidelberg, Schweiz
Staatsexamen am 20.11.2001 an der Universität Heidelberg

Promotionsfach: Innere Medizin
Doktorvater: Prof. Dr. med. K. Andrassy

In several clinical investigations it could be shown that the incidence of venous thromboembolism in patients with fractures and immobilization ranges from 20-40%. Even though, thromboprophylaxis is not generally recommended for patients with lower limb injuries. The Plaster Cast clinical trial demonstrated a moderate risk of venous thromboembolism (VTE) in otherwise healthy individuals (mean age 47 years) requiring immobilization in a plaster cast/brace after isolated minor lower limb injury (fracture; Achilles tendon rupture). In this placebo-controlled clinical study, low molecular weight heparin (LMWH, reviparin, 1750 IU subcutanously once daily) was given for the entire 5-6 week immobilization period. Study outcomes revealed reviparin to be effective and safe in reducing VTE (9.3% VTE in the reviparin versus (*vs*) 18.6% VTE in the placebo group, 50% relative risk reduction, $p<0.01$; no difference in bleeding).

It is now widely known that major trauma is associated with a hypercoagulable state. The process of hemostatic activation in major trauma patients is well investigated. In contrast, little data exist on the process of hemostatic activation in patients with lower leg injuries treated with brace or plaster cast immobilization. The laboratory study was a prospective, randomized, double-blind, placebo-controlled and parallel group comparison. The effect of thromboprophylaxis with reviparin on hemostatic markers was evaluated at baseline (day of randomization), treatment day 10-14 and day of cast removal in all 371 enrolled patients.

Mean thrombin-antithrombin (TAT) levels were higher than normal for all patients (4.02 ng/ml). Mean TAT levels were elevated in the fracture (4.31 ng/ml) compared to the tendon

rupture subgroup (2.76 ng/ml; $p<0.001$). For both VTE and non-VTE subgroups, TAT levels were still elevated at 10-14 days but were normal at brace removal. Median levels of tissue factor (TF) were elevated compared to a normal population (21.7 pg/ml) with excessive levels found in some patients equal to that found with total hip replacement. Median TF levels were more increased in the fracture compared to the soft tissue injury group (22.3 *vs* 13.8 pg/ml). TF levels remained elevated through to the post-brace period in the VTE subgroup. Surgery caused an increase of TAT but no effect on TF. Thrombomodulin and PAI-1 did not notably differ from normal levels.

Reviparin treatment decreased both elevated median tissue factor (TF) levels (reviparin: 21.7 to 2.1 to 12.6 pg/ml; placebo: 22.0 to 5.5 to 19.4 pg/ml) and thrombin-antithrombin (TAT) levels (reviparin: 1.79 to 0.97 to 0.59 ng/ml; placebo: 1.90 to 1.24 to 0.89 ng/ml). The greatest effect occurred in the first 2 treatment weeks ($p<0.001$ reviparin *vs* placebo, TAT change from baseline to day 10-14). Surgical patients benefited the most from reviparin treatment in terms of decreasing TF levels. Patients with VTE (n=52) had higher median baseline TF levels (49.1 *vs* 14.9 pg/ml; p=0.003). TFPI levels were higher in the reviparin group ($p<0.001$); there were no notable differences in thrombomodulin or PAI-1 levels.

Antibodies associated with heparin-induced thrombocytopenia (HIT) type II (anti-heparin-PF4-antibodies) were detected in 7/176 reviparin and 9/182 placebo-treated patients on day 14 (31% of all patients were pre-treated with LMWH (mostly enoxaparin) prior to randomization to reviparin/placebo).

In conclusion, the clinical efficacy of extended reviparin thromboprophylaxis at reducing VTE in minor lower limb trauma patients is associated with a reduction of the hypercoagulable state, defined by TF release and subsequent thrombin generation, without increasing the risk of heparin-induced thrombocytopenia. Patients undergoing surgery benefited most from reviparin treatment. Post-traumatic VTE in otherwise healthy individuals with lower limb injuries and plaster cast/brace immobilization was associated with a burst of TF release and thrombin generation that was sustained over weeks, with no fibrinolytic alterations as found with medical VTE. The hypercoagulable state was greater with fractures than with soft-tissue injuries, and greater with surgery than with conservative treatment.