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Individual Differences in Heparin Sensitivity and Their Effect on Heparin Anticoagulation During Arterial Vascular Surgery

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WHAT THIS PAPER ADDS

Although individual differences in heparin sensitivity exist, most patients undergoing arterial vascular surgery receive a fixed dose of heparin, despite no consensus existing on adequate heparin dosing. This prospective pilot study shows that inhibition of haemostatic activation was less profound in patients with reduced heparin sensitivity, which was most likely a result of heparin under dosing. Monitoring the anticoagulant effect of heparin should become part of clinical routine to optimise peri-procedural anticoagulation strategies during arterial vascular surgery.

Objectives: To investigate whether a fixed heparin dose results in adequate heparinisation levels and consequent inhibition of haemostatic activation in all patients.
Methods: This prospective clinical pilot study included 24 patients undergoing arterial vascular surgery. Individual heparin responsiveness was assessed using the Heparin Dose Response (HDR) test, while the activated clotting time (ACT) and heparin concentration were measured to monitor the peri-procedural degree of anticoagulation. Finally, peri-operative haemostasis was evaluated with rotational thromboelastometry (ROTEM).
Results: Eight patients were identified with reduced heparin sensitivity (RS group) and 16 patients with normal heparin sensitivity (NS group). Compared with the NS group, the RS group showed less prolonged ACTs after heparinisation with heparin concentrations below the calculated target heparin concentration. ROTEM revealed shorter clot formation times in the intrinsically activated coagulation test (INTEM) 3 min (114 ± 48 s vs. 210 ± 128 s) and 30 min after the initial heparin bolus (103 ± 48 s vs. 173 ± 81 s) in the RS group compared with the NS group. In the RS group, one patient developed a major thromboembolic complication.
Conclusions: This study shows that a third of the study population had reduced heparin sensitivity, which was associated with lower levels of heparinisation, and lower inhibition levels of clot initiation and clot formation. Identifying patients with reduced heparin sensitivity by monitoring the anticoagulant effect of heparin could decrease the risk of thrombotic complications after arterial vascular surgery.

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INTRODUCTION

Tissue injury during vascular surgery initiates a haemostatic response, potentially resulting in peri-operative thromboembolic complications, such as stroke or myocardial infarction.[1,2] Unfractionated heparin (UFH), a sulphated glycosaminoglycan, is administered to prevent these complications. Binding of UFH to the plasma protein antithrombin III (ATIII), causes a conformational change that results in ATIII activation. Activated ATIII then inactivates thrombin and other proteases involved in blood clot formation.[3]

Recently, Wiersema and colleagues[4] conducted a survey among Dutch vascular surgeons to evaluate current intra-operative anticoagulation practice during arterial vascular surgery. Analysis of 203 questionnaires revealed that almost all respondents used UFH, either in a fixed dose of 5000 IU or a weight based dose of 50–100 IU/kg. Previous studies in Europe[5–7] and the USA[8] showed that, despite the general use of UFH as intra-operative antithrombotic strategy in vascular surgery, the administered dose of UFH varies among centres. Additionally, as the individual heparin responsiveness varies widely in both vascular[9–13] and cardiac[14–16] surgery, patients may not receive an adequate

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dose. This is partly caused by an individual difference in the biological availability of heparin because of its binding to plasma proteins, macrophages, platelets, and endothelial cells.[15] Thrombocytosis (platelet count >300,000/mL), pre-operative heparin therapy, impaired liver function, low AT levels (<60%), high levels of Platelet Factor 4 (PF4), and elevated factor VIII levels also may be contributing factors.[14–17]

In cardiac surgery, the anticoagulant effect of UFH is routinely monitored by the activated clotting time (ACT).[18–20] Despite the general use of UFH in vascular surgery, ACT monitoring is no part of the clinical routine.[4–8] Consequently, it is unknown whether or not patients undergoing arterial vascular surgery receive adequate heparin dosing. Therefore, the objective of this study was to investigate whether a fixed dose of 5000 IU UFH in arterial vascular surgery provides sufficient anticoagulation for all patients. The individual heparin responsiveness of patients was measured and the individual heparin sensitivity was related to the levels of haemostatic activation.

MATERIALS AND METHODS

Study population and design

This prospective clinical study was performed in the departments of Cardiothoracic Surgery, Vascular Surgery and Anaesthesiology of the VU University Medical Centre (Amsterdam, the Netherlands). The protocol was approved by the Human Subjects Committee of the institution (HepaVasc; NL45906.029.13). All eligible patients provided written informed consent. Patient inclusion started in January 2014 and ended in February 2016. Patients between 18 and 85 years of age were eligible if having elective first time arterial vascular surgery that required heparinisation. Exclusion criteria were emergency or re-operations.

The primary study endpoint was the level of peri-procedural anticoagulation as measured by heparin concentration and activated clotting time (ACT). Blood samples for haemostatic measurements and routine laboratory testing were collected from a radial artery catheter after anaesthesia induction (Pre-HEP), 3 min (HEP-3), 30 min (HEP-30), and 60 min (HEP-60) after administering the heparin bolus, and before skin closure (SKIN). Blood for plasma determinations was centrifuged, and platelet free plasma was extracted and stored at -80 °C for further analysis.

Anticoagulation management and monitoring

The Haemostasis Management System (HMS, Medtronic, Minneapolis, MN, USA) was used to perform the heparin dose response (HDR) test to determine the individual response to heparin. This test measured the ACT in a blood sample that was either heparinised in vitro (1.5 and 2.5 IU/mL) or not heparinised (baseline) and responded linearly to increasing heparin concentrations.[14,15] The incremental clotting times were used to calculate the HDR slope, which helped to identify patients with reduced sensitivity to heparin (HDR slope ˂80 s/IU/mL).[17,21] Furthermore, the required heparin bolus to reach a target ACT of 200 s was calculated by means of the HDR slope, the target heparin concentration, and the estimated blood volume.[14,15] As recommendations for target ACT values are absent in guidelines, the target ACT value was based on previous measurements (unpublished data) of the lowest ACT value after administering the initial heparin bolus. All patients received a fixed intravenous dose of 5000 IU UFH prior to placement of the occluding arterial cross-clamp, after which the low range activated clotting time (LR-ACT; Haemochron, ITC Medical, Edison, NY) and the heparin concentration (Heparin Protamine Titration (HPT) test; Hepcon HMS, Medtronic) were measured to monitor the peri-procedural degree of anticoagulation.

Evaluation of peri-procedural haemostasis

Rotational thromboelastometry (ROTEM delta; TEM International, Munich, Germany) was used to assess clot activation, clot formation, clot polymerisation, and clot stability as well as the inhibition of the clotting cascade by heparin in whole blood by means of the intrinsically activated coagulation test (INTEM), extrinsically activated coagulation test (EXTEM), fibrin polymerisation test (FIBTEM), and the intrinsically activated coagulation test without heparin effect (HEPTEM).

Routine laboratory testing of the international normalised ratio (INR) of the prothrombin time (calcium thromboplastin) and the activated partial thromboplastin time (aPTT; cefaline) were determined using a STA-R instrument (Roche Diagnostics FmbH, Basel, Switzerland) in platelet free plasma. Other haemostatic parameters included haemoglobin and haematocrit levels and platelet count.

Plasma coagulation markers ATIII and factor Xa (FXa) activity were determined using a chromogenic assay (Werfen Benelux, Breda, the Netherlands), while PF4 was determined by ELISA (R&D systems, Minneapolis, MN, USA).

The thrombin generation assay was only performed in baseline samples (Pre-HEP), as heparin can interfere with this measurement. Citrated platelet free plasma was analysed with calibrated automated thrombography (CAT) as previously described.[22] Thrombin generation was assessed by lag time (min), peak height (nM), endogenous thrombin potential (ETP) (nM*min), and time to peak (min).

Other study parameters

Patient demographics included age, gender, and BMI, and pre-operative antithrombotic therapy. Surgical data were type of surgery and the amount of heparin administered. Clinical outcomes such as myocardial infarction, transient ischaemic attack (TIA), cerebral vascular incident (CVA), bleeding complications, and the need for emergency thrombectomy were also assessed.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software package 22.0 (IBM, New York, NY, USA) and

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