Hirudin versus heparin for anticoagulation in continuous renal replacement therapy

Abstract  Objective: To compare the efficacy and safety of hirudin and heparin for anticoagulation during continuous renal replacement therapy (CRRT) in critically ill patients.  
Design: Prospective, randomized controlled pilot study.  
Setting: Single centre; interdisciplinary intensive care unit at a university hospital.  
Patients: Seventeen patients receiving CRRT.  
Interventions: Patients were randomly allocated to two groups. Heparin group (nine patients): continuous administration of 250 IU/h heparin; dose was adjusted in 125 IU/h steps with a targeted activated clotting time (ACT) of 180–210 s. Hirudin group (eight patients): continuous infusion of 10 μg/kg/h hirudin, dose was adjusted in 2 μg/kg/h steps with a targeted ecarin clotting time (ECT) of 80–100 s. Observation time was 96 h.  
Measurements and main results: Measured filter run patency and haemofiltration efficacy did not significantly differ between the two groups. Three bleeding complications were observed in the hirudin group, none in the heparin group (P < 0.01). At the onset of bleeding, which occurred 60 or more hours after the start of therapy, only one patient was still under continuous hirudin administration but levels were either in therapeutic range or below.  

Conclusions: Hirudin can be used efficiently for anticoagulation in CRRT. Late bleeding complications may have been caused by possible hirudin accumulation, but this was not evident from hirudin plasma and ECT levels. Since bleeding complications were observed only in the presence of documented coagulation disorders, not only adequate drug monitoring but also the plasmatic and cellular coagulation status of the patient should be taken into consideration for adjusting hirudin dosage.  

Key words  Critically ill patients · Continuous haemofiltration · Anticoagulation · Heparin · Hirudin · Efficacy · Bleeding
Introduction

The incidence of acute renal failure (ARF) varies in critically ill patients but can be as high as 25% [1, 2, 3, 4]. A mortality rate between 50 and 90% has been reported in patients with ARF and multiple-organ dysfunction syndrome (MODS) [3, 4, 5]. Continuous renal replacement therapy (CRRT) has become the treatment of choice for ARF in the intensive care unit (ICU) [6, 7]. The goal for anticoagulation in CRRT is to maintain patency of the extracorporeal circuit and to prolong filter life and function in the presence of minimal or absent systemic effects. The blood-system interaction tends to activate plasmatic and cellular coagulation pathways leading to possible clot formation and membrane obstruction [8]. This is the reason why antithrombogenic therapy is required during extracorporeal blood purification techniques. Heparin is the most widely used substance for anticoagulation in CRRT [9]. Heparin exerts its anticoagulant effect mainly by enhancing the effect of antithrombin III (AT III) on thrombin inactivation. However, the anticoagulant effect may sometimes be insufficient, since heparin inactivates only free thrombin and not fibrin-bound thrombin [10, 11]. On the other hand, the increase in heparin dosage may result in bleeding complications [12]. A further problem may arise by the development of heparin-induced thrombocytopenia type II (HIT II) where further anticoagulation with heparin is contraindicated. The overall incidence of HIT II has been reported to be as high as 10% [13] with detection of heparin-induced antibodies against platelets in the patient’s plasma [14]. These and other adverse effects such as hypersensitivity reactions, skin necrosis, increase in liver enzymes and HIT II-independent thrombocytopenia have led to the search for a safer and more effective anticoagulant.

Hirudin, a polypeptide made by recombinant technology, and with a molecular weight of 7,000 Da, acts independently of cofactors, and directly inhibits bound and unbound thrombin. Its elimination half-life is 1–3 h, and the elimination pathway is >90% unmetabolized through the kidneys. In the presence of renal failure the half-life of hirudin is considerably prolonged [15, 16]. Hirudin is removed through haemofiltration membranes at a rate dependent on the sieving coefficient of the membrane used [17, 18]. In cases of ARF, hirudin accumulation may result in possible bleeding complications. Natural hirudin was utilized as a first anticoagulant in the early times of haemodialysis, but it was soon abandoned because of life-threatening hypersensitivity reactions. Recombinant hirudin, on the contrary, has been used safely and effectively for intermittent and continuous dialysis [10, 11, 19]. There are reports, however, of severe bleeding complications under hirudin anticoagulation for renal replacement therapy [20, 21]. The importance of adequate drug dosing and coagulation monitoring is considered to be essential to avoid accumulation. Activated partial thromboplastin time (aPTT) has been considered to be an unreliable monitoring parameter during hirudin anticoagulation, because it does not correlate with hirudin levels [22]. Ecarin clotting time (ECT), a whole-blood plasma clotting-time assay based on thrombin activation through the snake venom ecarin, has shown adequate dose-response curves [22]. As coagulation disorders with bleeding complications and episodes of filter clotting are depended either with heparin or with hirudin during CRRT, the aim of the present study was to evaluate the efficacy and safety of both regimes in a randomized, controlled, comparative trial carried out in patients treated with CRRT.

Materials and methods

After ethical committee approval and written informed consent from a legal representative, 20 critically ill patients with ARF and indication for CRRT were enrolled in this prospective, controlled, single-centre, open-labelled, randomized clinical trial. Exclusion criteria were age <18 years, pregnancy, acute head injury, acute bleeding and HIT II. Enrolled patients were randomly allocated into two groups. Three patients were excluded from the study after enrolment due to immediate surgery in one case and due to haemodynamic instability with pending surgery in two cases. Therefore, nine patients completed the study in the heparin group and eight patients in the hirudin group. All patients were sedated, mechanically ventilated and given additional therapy according to the ICU standard protocol. ARF was defined as a urine output <500 ml/24 h in spite of adequate fluid resuscitation and an increase in creatinine (normal: <115 \( \mu \)mol/l) and urea (normal: 2.3–7.6 mmol/l) of three-times the normal values.

A double-lumen venous catheter (Large-Bore catheter, 1.8 mm diameter, Arrow International, Reading Pa., USA) in the jugular, subclavian or femoral vein was used for vascular access. Continous pump-driven veno-venous haemofiltration (CVVH) was performed with a Polyflux 11 S, 1.1 m² haemofilter (Gambro Dialysatoren, Hechingen, Germany) and BM 11 + BM 14 equipment (Baxter, McGaw Park, III., USA). Pump-driven blood flow in the extracorporeal circuit was maintained at 80–150 ml/min. Ultrafiltrate was replaced by infusion of haemofiltration solution after the filter (post-dilution mode) at a rate of 1,000–2,000 ml/h. Anticoagulants were administered into the extracorporeal system before the haemofilter.

The heparin group received heparin (Liquemin N, Roche, Grenzach-Wyhlen, Germany) with an initial dose of 250 IU/h. The extracorporeal system was rinsed with 3 l of heparinized saline (10,000 IU of heparin) during the priming procedure. The anticoagulation therapy was monitored every 4 h using the activated clotting time (ACT) (HemoTEG ACT; Englewood Colo., USA). An ACT of 180–210 s was targeted and subsequent heparin dose adjustments were made using steps of 125 IU/h.

The hirudin group received 10 \( \mu \)g/kg/h hirudin (Relfludan, Aventis Pharma, Bad Soden im Taunus, Germany) initially. The extracorporeal system was rinsed during the priming procedure with 3 l of saline containing 100 \( \mu \)g of hirudin. The anticoagulation therapy was monitored every 4 h with the ECT (Thrombostat 2, Behnk Elektronik, Norderstedt, Germany). An ECT of 80–100 s was targeted and subsequent hirudin dose adjustments were made.