

*CONCEPT*

## **GUIDELINE FOR ANTICOAGULATION WITH UNFRACTIONATED HEPARIN AND LOW MOLECULAR WEIGHT HEPARINS DURING CONTINUOUS VENOVENOUS HEMOFILTRATION**

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This contribution is part of the guideline ‘Anticoagulation in continuous venovenous hemofiltration (CVVH)’ as being developed by the NVIC Committee Nephrology and Intensive Care of the NVIC

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### **INDEX**

#### **I ABSTRACT**

#### **II SAMENVATTING**

#### **III INTRODUCTION**

#### **II SEARCH METHODS**

#### **III UNFRACTIONATED HEPARIN**

#### **IV LOW MOLECULAR WEIGHT HEPARINS**

#### **V REFERENCES**

#### **I ABSTRACT**

During continuous venovenous hemofiltration (CVVH), the extracorporeal circuit is usually kept open by means of systemic anticoagulation. Traditionally, unfractionated heparin (UFH) was the drug of choice. With the introduction of low molecular weight heparins (LMWH), certain advantages over UFH have been advocated. In this guideline, pros and cons of both UFH and LMWH are discussed and the literature concerning the use of UFH and LMWH during CVVH is reviewed. Recommendations for dosing and monitoring are formulated, based on the levels of evidence of the studies reviewed.

#### **II SAMENVATTING**

Tijdens continue venoveneuze haemofiltratie (CVVH) wordt meestal systemische antistolling gebruikt om het extracorporele circuit open te houden. Traditioneel was ongefractioneerde heparine (UFH) het middel van keuze. Met de introductie van laagmoleculaire heparines (LMWH), werden bepaalde voordelen van LMWH ten opzichte van UFH geclaimd. In deze richtlijn worden de voor- en nadelen van UFH en LMWH besproken. Tevens wordt een overzicht gegeven van de literatuur betreffende het gebruik van UFH en LMWH tijdens CVVH. Op basis van de bewijslast van de betreffende literatuur zijn aanbevelingen geformuleerd betreffende dosering en monitoring.

### **III INTRODUCTION**

During continuous venovenous hemofiltration (CVVH), clotting in the extracorporeal circuit causes several problems. Clotting of the micropores diminishes the ultrafiltration rate and thus the efficacy of the treatment. Clotting of the hollow fibers causes a rise in prefilter pressure, which leads to more alarms and a need for closer supervision of the attending nurse. When clot formation occurs in the circuit and the blood cannot be returned to the patient, this will result in a loss of approximately 300 ml. Finally, shorter use of a circuit entails higher costs. For all these reasons, most intensive care units use continuous systemic anticoagulation to keep the extracorporeal circuit open. The ideal anticoagulant would have optimal antithrombotic activity, minimal bleeding complications, no systemic complications, a short half life, good possibilities for monitoring, possibility to antagonize and a low price. In this respect, unfractionated heparin (UFH) has a rather good profile. Although the experience with low molecular weight heparins (LMWH) as anticoagulant during CVVH is limited, several studies have reported that LMWH and UFH have a comparable efficacy and safety when used during CVVH.

### **II SEARCH METHODS**

We performed an extensive search of the literature by means of the MEDLINE database over the period from 1977 until November 2002. As Mesh Heading key words and text words we used 'hemofiltration', 'haemofiltration', 'heparin', 'low molecular weight heparin', 'LMWH' and their combinations. The retrieved studies were limited to 'human'. The references of the selected articles were reviewed for further possibly relevant studies. Articles were included notwithstanding the type of publication or the language. We exclusively selected studies concerning continuous venovenous hemofiltration or continuous venovenous hemodiafiltration in critically ill adult patients. We excluded studies concerning hemodialysis and continuous arteriovenous hemofiltration and studies concerning patients with chronic renal failure. For the final analysis, we selected those studies in which clinically relevant endpoints have been investigated, such as mortality, circuit survival time, thrombo-embolic and bleeding complications and necessity of transfusion. We analysed the literature and formulated recommendations according to the procedure of the NVIC Committee Guideline Development (1).

### **III UNFRACTIONATED HEPARIN**

UFH is still the most commonly used agent for prevention of coagulation in the extracorporeal circuit during CVVH. The action of UFH is based on inhibition of factors Xa and IIa. UFH has an anti-Xa versus anti-IIa ratio of 1:1 (2). When UFH is administered intravenously, its action starts 2 minutes after injection. UFH is taken up by the reticulo-endothelial system and is metabolised by the liver. Metabolites are normally eliminated by the renal route. Plasma half life varies from 30 minutes to 3 hours. However, the pharmacokinetics of UFH can be unpredictable in the individual patient. This is caused by the nonspecific binding of UFH to proteins and cells (3). Since UFH is highly negatively charged, it can bind to a variety of plasma proteins (including lipoproteins and fibrinogen) as well as to proteins secreted by platelets (e.g. platelet factor 4). As some of these proteins are acute phase reactants, their levels can be elevated in critically ill patients. The variability in plasma levels of heparin-binding proteins is responsible for the unpredictable anticoagulant response of UFH.

There is good evidence for a relationship between heparin dose and both efficacy and bleeding (3). The heparin concentration can be measured by protamine titration or antifactor

Xa (aXa) level. The anticoagulant effect of heparin is usually monitored by the activated partial thromboplastin time (APTT). However, there is a moderate correlation between APTT levels and heparin concentration. In one study, more than two thirds of patients with subtherapeutic APTT levels had therapeutic heparin levels (3). In patients with a subtherapeutic APTT response despite high doses of heparin, the heparin concentration can reliably be monitored by aXa assay (3). It is prudent to maintain the APTT below levels corresponding with heparin concentrations of 0.4 U/mL (by protamine titration) or 0.7 U/mL (by aXa) (3).

The anticoagulant action of UFH can be antagonized by protamine sulfate. Each mg of protamine sulfate neutralizes approximately 85 – 110 IU of UFH.

A disadvantage of UFH is that 5 to 10% of the treated patients develop heparin-induced thrombocytopenia (HIT). Ten to twenty percent of the HIT patients develop heparin-induced thrombocytopenia and thrombosis (HITT), which can cause medium to large vessel occlusion, leading to gangrene (4).

Several authors have described the use of UFH during CVVH (5-11,18). The results of these studies are summarized in Table 1. Generally, an UFH maintenance dose of 5-10 IU/kg/h is used, either or not preceded by a loading dose of 1000-5000 IU. Two authors aim at a therapeutic prolongation of APTT or activated clotting time (ACT) (5,9). However, the risk of bleeding during UFH treatment is related to the dose of UFH given (3). In a recently conducted prospective cohort study, circuit survival time was not correlated with the APTT (11). Aiming at a therapeutic prolongation of the APTT (1.5 – 2.3 times control) probably increases the risk of bleeding, without prolonging circuit survival time. Ronco et al found a 4-6% bleeding incidence with an incidence of repeated filter clotting of 2-3%, using UFH in an initial rate of 8 IU/kg/h, aiming at an APTT 1.3 – 1.4 times control (12).

As bleeding is considered a more serious threat to the patient than filter clotting, we do not recommend a therapeutic prolongation of APTT.

***Recommendation*** Based on the available studies, we recommend priming of the circuit with 5000 IU UFH, followed by a loading dose of 1000 – 5000 IU and a maintenance dose of 5-10 IU/kg/h UFH, aiming at an APTT up to 1.4 times the upper limit of normal. When an APTT prolongation is not reached, the UFH dose should not be raised above 10 IU/kg/h (level of recommendation D) (Table 3).

#### **IV LOW MOLECULAR WEIGHT HEPARINS**

The mechanism of action of low molecular weight heparins (LMWH) is similar to that of UFH. However, because of their reduced chain length, LMWH exhibit a relatively lower anti factor IIa activity than UFH. The different LMWH also differ in the ratio of anti-Xa versus anti-IIa inhibition (2). The pharmacokinetics of LMWH are more predictable than those of UFH because of reduced nonspecific binding to plasma proteins (3). In contrast to UFH, LMWH exhibit linear pharmacokinetics with proportionality between anti-Xa plasma concentration and dose, stationary distribution volume and clearance processes (13). The distribution volume of LMWH is close to the blood volume. LMWH are partially metabolised by desulphatation and depolymerisation. Urinary excretion of anti-Xa activity is between 5 and 10% of the injected dose (13). Clearance by CVVH is also insignificant (14). LMWH differ in the extent of their non-renal clearance. Because of these differences, the clinical profile of a given LMWH cannot be extrapolated to another one (2). The half life of LMWH is considerably longer than that of UFH (2-4 hours versus 0.5-3 hours for UFH). This could be explained by the fact that LMWH do not bind to endothelial cells (3). Furthermore, as the anti-Xa effect of LMWH is stronger than their anti-IIa effect, this implicates that the

anticoagulant effect of LMWH can only partially be neutralized by protamine sulfate. The anticoagulant activity of LMWH can be monitored by determining the anti-Xa activity, but routine monitoring is not necessary. Moreover, the correlation between anti-Xa level and circuit survival time was denied in several studies (15,16). Although the price of LMWH is fivefold the price of UFH, one saves the costs of routine APTT monitoring when using LMWH, which makes the daily costs of the use of LMWH and UFH similar. Another advantage of LMWH over UFH is the lower incidence of HIT (17).

Experience with LMWH during CVVH is limited. An overview is presented in table 2. In the Netherlands, only nadroparin and dalteparin have been registered for the use in extracorporeal circuits. For dalteparin, different doses have been used. De Pont et al. used 400 IU dalteparin for priming, followed by a loading dose of 2000 IU (25 IU/kg) and a maintenance dose of 320 IU/h. This resulted in a median circuit survival time of  $15.4 \pm 7.4$  h without clinically important bleeding episodes (16). In a pilot study, Reeves et al. used a dalteparin loading dose of 15-25 IU/kg, followed by a maintenance dose of 5 IU/kg/h. This resulted in a median time to circuit failure of  $22.5 \pm 4.3$  h without bleeding complications. In their controlled study, Reeves et al. used a dalteparin loading dose of 20 IU/kg, followed by a maintenance dose of 10 IU/kg/h. This resulted in a mean time to circuit failure of  $46.8 \pm 5$ h, with two episodes of significant bleeding in 25 patients (8%) (5). In summary, an acceptable circuit survival time with optimal safety can be reached with a dalteparin loading dose of 15-25 IU/kg, followed by a maintenance dose of 5 IU/kg/h. As nadroparin has been shown to be bioequivalent to dalteparin (16), the same dose can be used.

***Recommendation*** *We recommend either nadroparin or dalteparin priming with 400 IU, followed by a loading dose of 15-25 IU/kg, and a maintenance dose of 5 IU/kg/h (level of recommendation C) (Table 3).*

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**Table 1.** Studies on the use of unfractionated heparin during continuous renal replacement therapy in critically ill patients with acute renal failure

Author Year (ref)	Design	Level of evidence	Hemofiltration mode	UFH dosage	N	Circuit survival time	Other results	Bleeding complications
Tan 2000 (11)	prospective cohort study no anticoagulation vs low dose UFH	III	CVVH Qb 200-300 ml/min predilution	priming 5000 IU UFH maintenance UFH 5-10 IU/kg/h aim: normal APTT	12	19.5 h (95% CI 14.2 – 23.8)		none
Reeves 1999 (5)	RCT LMWH vs UFH	II	CVVHD Qs 500 ml/h predilution	loading dose UFH 2000-5000 IU, maintenance 10 IU/kg/h aim: APTT 70-80 s	22	51.7 ± 7.5 h		4 episodes of significant bleeding
Leslie 1996 (6)	repeated crossover undiluted (100 IU/ml) vs diluted (10 IU/ml) UFH	II	CVVHD	Undiluted UFH (100 IU/ml) vs diluted (10 IU/ml) UFH	18	20.1 ± 14.6 h for 100 IU/ml and 21.4 ± 19.2 h for 10 IU/ml		
Gretz 1995 (18)	uncontrolled study of low dose UFH	IV	CVVH Qb 100 ml/min predilution	priming 20,000 IU UFH in 2 liter NaCl 0.9%, followed by flushing with 1-2 L NaCl 0.9% maintenance UFH 135 IU/kg/day	27		ACT ± 150 s, APTT ± 40 s. Decrease in platelet count (from 119 ± 110 to 100 ± 66). Increase in fibrinogen (from 476 ± 112 to 511 ± 112 mg/dl)	not mentioned
Stefanidis 1995 (9)	uncontrolled study correlating FST to UFH dose	IV	CVVH Qb 120 ml/min Qs 1.25 l/h postdilution	UFH maintenance 750 ± 467 IU/h aim: ACT > 110 s	60	30 ± 25 h	CST correlated with ACT if < 120 s, but not with ACT if > 120s	not mentioned
Martin 1994 (10)	retrospective study comparing no UFH to 100-700 IU/h and > 700 IU/h	III	CVVH Qb 100 – 150 ml/min Qs 0.8 – 1.3 l/h postdilution	priming 5000 IU UFH in 2 liter NaCl 0.9% loading dose UFH 1000 – 2000 IU maintenance UFH 100 – 2000 IU/h	218	24.7 ± 13.2 h for 100-700 IU/h and 23 ± 9.6 h for ≥ 700 IU/h		deaths attributed to bleeding 7.2% in UFH 100 – 700 IU/h, 10% in UFH > 700 IU/h
Langen-ecker 1994 (7)	RCT UFH vs PGI <sub>2</sub> and UFH + PGI <sub>2</sub>	II	CVVH predilution	no loading dose maintenance UFH 6 ± 0.3 IU/kg/h	13	14.3 ± 3 h		no major bleeding complications
Bellomo 1993 (8)	RCT low dose pre filter UFH vs regional anticoagulation	II	CVVHD Qb 150 ml/min	Maintenance UFH 500 IU/h	33	31.4 h		one case of prolonged oozing from the catheter insertion site

UFH, unfractionated heparin; N, number of patients; CVVH, continuous venovenous hemofiltration; Qb, blood flow; APTT, activated partial thromboplastin time; RCT, randomised controlled trial; LMWH, low molecular weight heparin; CVVHD, CVVH + dialysis; Qs, substitution flow; ACT, activated clotting time; CST, circuit survival time; PGI<sub>2</sub>, prostaglandin I<sub>2</sub>, prostacyclin.

**Table 2.** Studies on the use of low molecular weight heparins during continuous renal replacement therapy in critically ill patients with acute renal failure.

Author Year (ref)	Design	Level of evidence	Drug	Hemofiltration mode	Dosage	N	Circuit survival time	Other results	Bleeding complications
de Pont 2000 (16)	RCT Cross-over nadroparin vs dalteparin	II	nadroparin  dalteparin	HV-CVVH Qb 200 ml/min Qs 4000 ml/h postdilution	priming 410 IU loading dose 2050 IU maintenance 328 IU/h  priming 400 IU loading dose 2000 IU maintenance 320 IU/h	32	median 18 h	nadroparin and dalteparin are bioequivalent	no clinically important bleeding complications
Reeves 1999 (5)	RCT UFH vs dalteparin	II	dalteparin	CVVHD Qb 120 ml/min Qs 500 ml/h predilution	loading dose 20 IU/kg maintenance 10 IU/kg/h	47	median for dalteparin 46.8 ± 5 h	costs 10% higher for dalteparin vs UFH	two episodes of significant bleeding
Journois 1990 (15)	RCT UFH vs enoxaparin vs enoxaparin +PGI <sub>2</sub>	II	enoxaparin	CVVH Qb 110 ml/min Qs 700 ml/h postdilution	priming 0.1 mg/kg maintenance 1.2 mg/kg/day	15	not mentioned	greater decline in filter permeability index for UFH vs enoxaparin	no bleeding complications

N, number of patients; RCT, randomized controlled trial; HV-CVVH, high-volume continuous venovenous hemofiltration; Qb, blood flow; Qs, substitution flow; UFH, unfractionated heparin; CVVHD, continuous venovenous hemofiltration and dialysis; PGI<sub>2</sub>, prostaglandin I<sub>2</sub>; CVVH, continuous venovenous hemofiltration.

**Table 3.** Recommended dosing schemes for the use of heparins during continuous venovenous hemofiltration.

	<b>Priming</b>	<b>Loading dose</b>	<b>Maintenance dose</b>	<b>Level of recommendation</b>	<b>References</b>
UFH	5000 IU	1000 – 5000 IU	5-10 IU/kg/h aim : APTT up to 1.4 times the upper limit of normal	D	5, 7, 10, 11
LMWH: dalteparin or nadroparin	400 IU	15-25 IU/kg	5 IU/kg/h	C	5, 16

UFH, unfractionated heparin; LMWH, low molecular weight heparin