

GUIDELINES FOR ANTICOAGULATION WITH UNFRACTIONATED HEPARIN AND LOW MOLECULAR WEIGHT HEPARINS DURING CONTINUOUS VENOVENOUS HEMOFILTRATION IN THE INTENSIVE CARE UNIT

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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

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ABSTRACT

During continuous venovenous hemofiltration (CVVH), thrombosis in the extracorporeal circuit is usually prevented by means of systemic anticoagulation. Traditionally, unfractionated heparin (UFH) was the drug of choice. After the introduction of low molecular weight heparin (LMWH), certain advantages over UFH have been advocated. In these guidelines, 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 presented, based on the levels of evidence of the studies reviewed.

SAMENVATTING

Tijdens continue venoveneuze haemofiltratie (CVVH) wordt meestal systemische antistolling gebruikt om het extracorporele systeem open te houden. Traditioneel was ongefractioneerde heparine (UFH) het middel van keuze. Met de introductie van laagmoleculaire heparine (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.

I 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 by the attending nurse. When the system clots and the blood cannot be returned, this means approximately 300 ml blood loss for the patient. Finally, shorter use of a system 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 October 2005. 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 had been investigated, such as mortality, filter survival time, thrombo-embolic and bleeding complications and necessity of blood 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 metabolized by the liver. Metabolites are normally eliminated by the renal route. The plasma half life of UFH varies from 30 minutes to 3 hours. However, the pharmacokinetics of UFH can be unpredictable in the individual patient. This is mainly 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 monitored by the activated partial

thromboplastin time (APTT) when usual therapeutic doses are used and by the activated clotting time (ACT) when higher doses are used in association with therapeutic interventions (4). 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 advised 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 (5).

Several authors have described the use of UFH during CVVH in a controlled study (6-13). 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. Three authors aim at a therapeutic prolongation of APTT or ACT (6,7,9). However, the risk of bleeding during UFH treatment is related to the dose of UFH given (3). In a recently conducted prospective cohort study, filter survival time was not correlated with the APTT (8). Aiming at a therapeutic prolongation of the APTT (1.5 – 2.3 times control) probably increases the risk of bleeding, without prolonging filter survival time. Indeed, in the studies aiming at therapeutic prolongation of APTT or ACT, bleeding complications were reported (6,7,9). 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 the upper limit of normal (14).

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 filter with 5000 IU UFH, followed by a maximum loading dose of 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).

Aanbeveling Op basis van de beschikbare studies adviseren wij priming van het filter met 5000 IE ongefractioneerde heparine, gevolgd door een maximale oplaaddosis van 5000 IE en een onderhoudsdosis van 5-10 IE/kg per uur ongefractioneerde heparine, met een streef APTT tot 1.4 maal de bovengrens van de normaawaarde. Als er geen APTT verlenging wordt bereikt, moet de dosering ongefractioneerde heparine niet verder worden verhoogd dan 10 IE/kg per uur (aanbevelingsniveau D) (Tabel 3).

IV LOW MOLECULAR WEIGHT HEPARINS

The mechanism of action of low molecular weight heparins (LMWHs) is similar to that of UFH. However, because of their reduced chain length, LMWHs exhibit a relatively lower anti factor IIa activity than UFH. The different LMWHs also differ in the ratio of anti-Xa versus anti-IIa inhibition (2). The pharmacokinetics of LMWHs are more predictable than those of UFH because of reduced nonspecific binding to plasma proteins (3). In contrast to UFH, LMWHs exhibit linear pharmacokinetics with proportionality between anti-Xa plasma

concentration and dose, stationary distribution volume and clearance processes (15). The distribution volume of LMWHs is close to the blood volume. LMWHs are partially metabolized by desulphatation and depolymerisation. Urinary excretion of anti-Xa activity is between 5 and 10% of the injected dose (15). Clearance by CVVH is also insignificant (16). LMWHs 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 LMWHs 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 LMWHs do not bind to endothelial cells (3). Furthermore, as the anti-Xa effect of LMWHs is stronger than their anti-IIa effect, this implies that the anticoagulant effect of LMWHs can only partially be neutralized by protamine sulfate. The anticoagulant activity of LMWHs can be monitored by determining the anti-Xa activity, but routine monitoring is not necessary. Moreover, the correlation between anti-Xa level and filter survival time was denied in several studies (17,18). Although the price of LMWHs is fivefold the price of UFH, one saves the costs of routine APTT monitoring when using LMWHs, which makes the daily costs of the use of LMWHs and UFH similar. Another advantage of LMWHs over UFH is the lower incidence of HIT (19).

Experience with LMWHs 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 filter survival time of 15.4 ± 7.4 h without clinically important bleeding episodes (18). 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 filter failure of 22.5 ± 4.3 h without bleeding complications. In a study comparing UFH to LMWH, 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 filter failure of 46.8 ± 5 h, with two episodes of significant bleeding in 25 patients (8%) (9). Nadroparin was used by van der Voort and De Pont in maintenance doses of 475 IU/h and 328 IU/h respectively, leading to median and mean circuit survival times of 39.5 h and 15 ± 9.9 h respectively (20,18).

In summary, an acceptable filter 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 (18), 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).*

Aanbeveling *Wij bevelen priming met 400 IU hetzij nadroparine of dalteparine aan, gevolgd door een oplaaddosis van 15-25 IE/kg, en een onderhoudsdosis van 5 IE/kg per uur (aanbevelingsniveau C) (Tabel 3).*

V CHOICE FOR UFH OR LMWH

The choice for UFH or LMWH has to be made by each institution individually, as it depends on experience, monitoring facilities and budget. To facilitate this decision making, pro and con arguments are listed in Table 4.

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Table 1. Controlled 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
VargasHein 2004 (6)	prospective RCT intermittent hirudin vs continuous heparin	II	CVVH Qb 80-150 ml/min Qs 1000-1500 ml/h Postdilution	UFH 250 IU/h. Increase according to ACT Aim: ACT 180-210 s.	26	UFH median 13h (4-63) Hiudin 11h (4-30) p=0.18		Bleeding episodes: 2 in the UFH group (14%) 0 in the hirudin group (0%)
Monchi 2004 (7)	prospective RCT citrate vs heparin cross-over	II	CVVH Qb >150 ml/min Qs 35 ml/kg/h Postdilution	loading dose UFH 2000-5000 IU, maintenance 1000 IU/h aim: APTT 60-80 s	20	UFH median 40h (interquartile range 17-48) Citrate 70h (44-140) p=0.0007	Patients transfused UFH group 63%, citrate group 38% p=0.03 Units RBC transfused per CVVH day UFH 1.0 (0-2), citrate 0.2 (0-0.4), p=0.0008	Major bleeding: 1 out of 23 UFH sessions (4%) 0 out of 26 citrate sessions (0%)
Tan 2000 (8)	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	26	UFH mean 19.5 h (95% CI 14.2 – 23.8) no anticoagulation mean 32h (95%CI 20-44.4) p=0.017		none
Reeves 1999 (9)	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	47	UFH mean 51.7 ± 7.5 h Dalteparin mean 46.8 ± 5.07 h (NS)		Episodes of significant bleeding: 4 in the UFH group (18%), 2 in the dalteparin group (8%)
Leslie 1996 (10)	repeated crossover undiluted (100 IU/ml) vs diluted (10 IU/ml) UFH	II	CVVHD	Priming 5000 IU UFH/1 Undiluted UFH (100 IU/ml) vs diluted (10 IU/ml) UFH	26	20.1 ± 14.6 h for 100 IU/ml and 21.4 ± 19.2 h for 10 IU/ml (NS)	Pre heparin APTT was predictive of filter life (p=0.03)	Complication rate 5.5%
Martin 1994 (11)	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	255	22.1 ± 14.8 h for no anticoagulation, 24.7 ± 13.2 h for UFH 100-700 IU/h and 23 ± 9.6 h for UFH ≥ 700 IU/h (NS)		Deaths attributed to bleeding : 7.2% in UFH 100-700 IU/h, 10% in UFH >700 IU/h
Langen- ecker 1994 (12)	RCT UFH vs PGI ₂ and UFH + PGI ₂	II	CVVH predilution	no loading dose maintenance UFH 6 ± 0.3 IU/kg/h	46	UFH 14.3 ± 3 h PGI ₂ 17.8 ± 1.9 h UFH + PGI ₂ 22 ± 0.96		No major bleeding complications
Bellomo 1993 (13)	RCT low dose pre filter UFH vs regional anticoagulation (UFH/protamine)	II	CVVHD Qb 150 ml/min	Maintenance UFH 500 IU/h	64	Low dose UFH mean 31.4 h (23.2-39.6) Regional anticoagulation mean 40.5 h (28.7-52.3) (NS)		One case of prolonged oozing from the catheter insertion site

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 implications
Van der Voort 2005 (20)	Prospective cross-over study nadroparin vs UFH/protamine	II	nadroparin	CVVH Qb 200 ml/min Qs 3000 ml/h postdilution	priming 5700 IU/l loading dose 2850 IU maintenance 475 IU/h	15	nadroparin 39.5 (IQR 8.5-48) UFH/protamine 12.3 (7.5-27) p=0.045		not mentioned
de Pont 2000 (18)	RCT Cross-over nadroparin vs dalteparin	II	nadroparin dalteparin	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	nadroparin mean 15.0 ± 9.9 h dalteparin mean 15.4 ± 7.7 h	nadroparin and dalteparin are bioequivalent	no clinically important bleeding complications
Reeves 1999 (9)	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	UFH mean 51.7 ± 7.5 h Dalteparin mean 46.8 ± 5.07 h (NS)	costs 10% higher for dalteparin vs UFH	episodes of significant bleeding: 4 in the UFH group, 2 in the dalteparin group
Journois 1990 (17)	RCT UFH vs enoxaparin vs enoxaparin +PGI ₂	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	IPM _{1/3} UFH 15.1 ± 2.4 h Enoxaparine 18.3 ± 3.1h (p < 0.05) PGI ₂ + enoxaparine 28.2 ± 4.2 h (p < 0.05)	no bleeding complications

Ref, reference; N, number of patients; RCT, randomized controlled trial; Qb, blood flow; Qs, substitution flow; UFH, unfractionated heparin; CVVHD, continuous venovenous hemofiltration and dialysis; PGI₂, prostaglandin I₂; CVVH, continuous venovenous hemofiltration; IPM_{1/3}, time needed to reach 1/3 of the initial membrane permeability index; [IQR, interquartile range.](#)

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

	Priming	Loading dose	Maintenance dose	Level of recommendation	References
UFH	0 - 5000 IU	1000 – 5000 IU	5-10 IU/kg/h aim : APTT up to 1.4 times the upper limit of normal	D	8,9
LMWH: dalteparin or nadroparin	400 IU	15-25 IU/kg	5 IU/kg/h	C	9,18,20

UFH, unfractionated heparin; LMWH, low molecular weight heparin

Table 4. Pro and con arguments to make the choice for UFH ofr LMWH

UFH		LMWH	
Pro	Con	Pro	Con
Half life 30 minutes to 3 hours			Half life 2 to 4 hours
Possibility to antagonize with protamine			Possibility to antagonize only partially
Price per day €1.92			Price per day €10.14
	Pharmacokinetics individually unpredictable	Linear pharmacokinetics	
	Moderate correlation between APTT level and UFH concentration	Routine monitoring unnecessary	
	HIT incidence 9.1 - 20.7%	HIT incidence 2.8 - 7.5%	