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Low Molecular Weight Heparins as Thromboprophylaxis in Patients Undergoing Hemodialysis/Hemofiltration or Continuous Renal Replacement Therapies

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Abstract: Low molecular weight heparins (LMWHs) have potential advantages over unfractionated heparin (UFH). They interact less with platelets and may induce less bleeding. The risk for heparin induced thrombocytopenia is less, and the effect on serum lipids is favourable. The half-life is longer, allowing for one single bolus dose at start of hemodialysis (HD). In addition, LMWH is found to result in lower plasma potassium in HD patients compared to UFH.

LMWHs have an established role in HD and hemofiltration (HF), but the reports on their efficacy and safety during continuous renal replacement therapy (CRRT) are scarce.

Key words: Low molecular weight heparin; dalteparin; nadroparin; enoxaparin; tinzaparin; reviparin; logiparin; parnaparin; ardeparin; bemiparin; hemodialysis; hemofiltration; hemodiafiltration; continuous renal replacement therapy

Abbreviations: Anti-FXa = anti-Factor Xa, AT = antithrombin, CRRT = continuous renal replacement therapy, CVVHD = continuous venovenous hemodialysis, CVVHF = continuous venovenous hemofiltration, ECC = extracorporal circuit, HD = hemodialysis, HDF = hemodiafiltration, HF = hemofiltration, HIT = heparin induced thrombocytopenia, IU = international unit, LMWH = low molecular weight heparin, MW = molecular weight, UFH = unfractionated heparin

LMWHs in Hemodialysis and Hemofiltration

Activation of coagulation and of platelets takes place when blood comes in contact with the surface of lines and filter in the extracorporal circuit (ECC). Anticoagulant treatment is mandatory during hemodialysis (HD) to prevent clotting in the ECC. Traditionally, the anticoagulation regimen during HD consisted of an intravenous bolus dose of unfractionated heparin (UFH) followed either by continuous infusion or a subsequent bolus dose during dialysis. However, during the last 10 years UFH has increasingly being replaced by low molecular weight heparin (LMWH), which are developed by fractionating UFH.

LMWHs have a relative molecular weight (MW) of 2500-6500 D, and the half-life is approximately two to three times longer than that of UFH after intravenous infusion in humans. Their prolonged half-lives enable single bolus administration at the start of HD. LMWH bind to antithrombin (AT), accelerating the inhibitory effect of AT on factor Xa (FXa) and to a lesser extent of factor IIa (thrombin), thus the anti-FXa/anti-IIa ratio is increased compared to UFH. Different LMWHs vary in their MW distribution and due to that they differ in the anti-FXa/anti-thrombin specificities and pharmacokinetics. As a consequence, clinical results with one LMWH can not be extrapolated to another compound, and each LMWH preparation should be tested in HD to define its efficacy, safety and appropriate dosage regimen.

LMWHs have several potential advantages over UFH. They interact less with platelets and the vessel wall, and some studies have shown that patients treated with an LMWH needed less blood cell transfusions [1, 2]. Moreover, the risk of heparin induced thrombocytopenia (HIT) is also smaller [3]. This complication is reported to occur in more than 3% of HD patients receiving UFH and is associated with heparin-dependent IgG antibodies against anti-platelet factor 4 –heparin complex. It may result in excess clot formation in the dialyser and ECC or other venous or arterial thrombotic events [4]. LMWHs should also be avoided in these patients due to cross-reaction with heparin-induced antibodies. The low-molecular weight heparanoid danaparoid (Orgaran) or recombinant hirudin can be employed as anticoagulants during HD in these patients [5]. However, these compounds will not be discussed further in this review.

The effect of LMWHs and of UFH on serum lipid profiles have been investigated in several studies, and in most of these, serum lipid profiles are found to be improved with the use of LMWHs [5]. However, it has not been shown if LMWH-treatment leads to less cardiovascular disease in HD patients.

In addition, LMWH-treatment results in a lowering of plasma potassium in HD patients compared to UFH, which is of clinical significance

Table 1. Clinical studies evaluating the use of LMWH in hemodialysis and hemofiltration[a].

LMWH	Number (No.) clinical studies	Total no. patients studied	No. studies excluding patients on oral anticoagulants and anti-platelet drugs	No. studies with grading of clotting in the dialyzer and/or bubble trap	AFXa-activity level needed to avoid clotting[b]
Dalteparin [2, 6-20]	16	422	6	7	0.4-0.5
Nadroparin [21-27]	7	128	0	5	0.4
Enoxaparin [28-30]	3	82	1	2	0.4
Tinzaparin [31-35]	5	302	1	4	0.4[c]-0.5
Reviparin [36, 37]	2	25	0	0	0.8
Logiparin [38]	1	8	1	1	0.3[d]
Parnaparin	0				
Ardeparin	0				

[a] Only clinical trials published since 1985 in International journals in English language and given an official impact factor. Studies mainly evaluating the effect on lipids are not considered in this table.
[b] Usually measured at the end of HD. Only anti-FXa measured with a chromogenic substrate are reported here.
[c] One hour after start of HD (Simpson 1996).
[d] 4 hours after start of HD, clots were not avoided (Koutsikos, 1996).

since hyperkalemia is a common problem in HD patients [5]. Finally, the administration of a single bolus dose LMWH at start of HD is practical and time saving for the staff.

Clinical Trials on LMWHs in Hemodialysis

A Medline search of clinical trials performed between 1985 and the first part of 2003 of different LMWHs in HD published in International journals in English language and given an official impact factor, resulted in a total of 34 studies, see Table 1. For parnaparin and ardeparin there was little or no documentation for use in HD. Thirteen of the studies had a randomized crossover design, 10 were non-randomized crossover and 6 were randomized.

Efficacy

In all but one of the studies the anticoagulation efficacy was evaluated by clot formation in the dial-

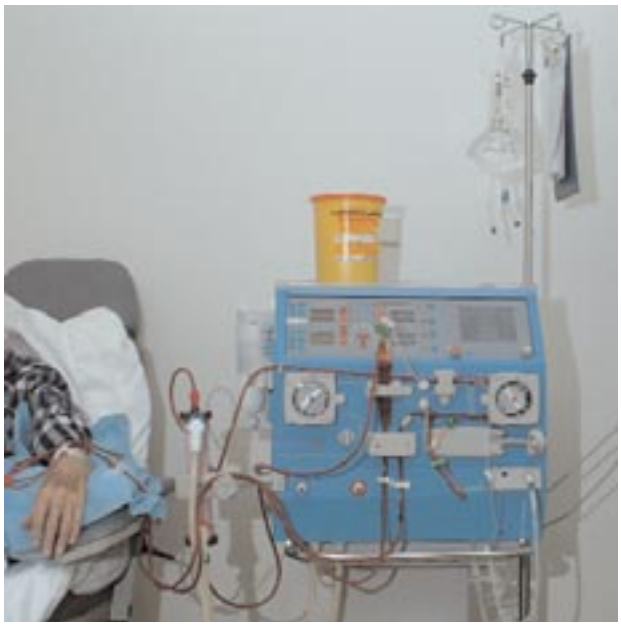

Fig. 1A. Intermittent hemodialysis, blood lines from the A-V fistula on the left forearm.

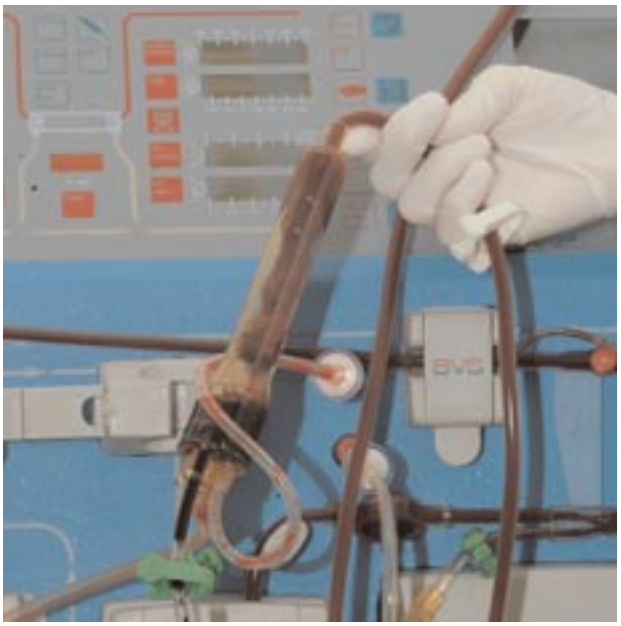

Fig. 1B. Clotting in the venous bubble trap inducing stop in dialysis in a patient at the end of a 4 hour hemodialysis session. The patient lost the blood volume in the filter and lines (about 200 ml).

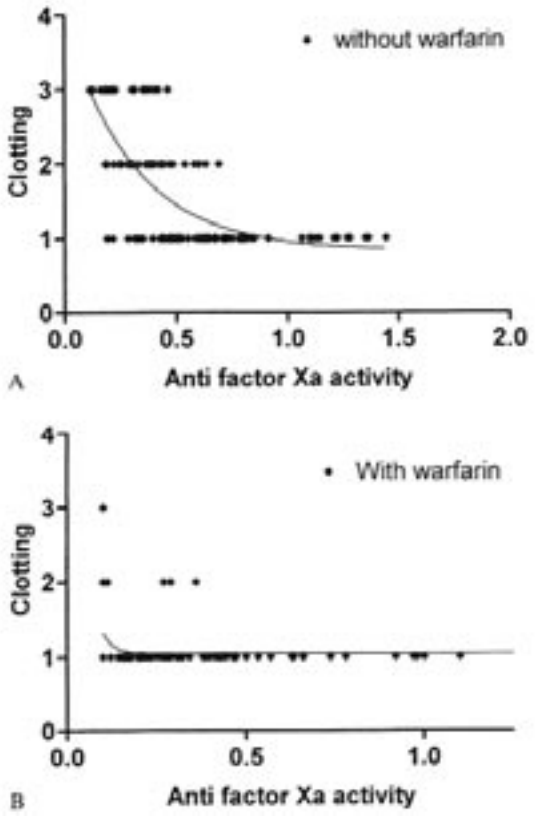

Fig. 2A and 2B. The one-exponential relationship between clotting in the bubble trap and anti-FXa activity (IE/ml). The correlation is statistically highly significant both in the six patients without warfarin (R = 0.67, A) and in the six patients receiving warfarin, where the curve is displaced to the left (R = 0.32, B). From the study of Sagedal et al., [17]. (The figure is printed with permission from Oxford University Press.)

yser and/or bubble trap or lines. In one study clinical clotting was evaluated by depletion of anticoagulant TFPI and found that UFH was more prothrombotic than enoxaparin [28]. Hofbauer et al. evaluated membrane-associated clotting very elegantly by using scanning electron micoscope [11]. In a few studies the fibre bundle volume of the dialyser was determined [12, 23]. However, these methods may be difficult to perform, and due to that a visual evaluation of clot formation in the bubble trap and/or dialyser is most often performed in clinical trials. In 19 of these 34 studies a grading of visually evaluated clotting in the bubble trap and/or dialyser was performed. Visible clotting in the tubing aspect and the dialyser aspect have been evaluated separately in some studies. In others, visually evaluated clotting in the dialyser and the bubble trap were evaluated on the same scale, indicating that clots in the bubble trap is more serious than a few clotted fibers in the dialyser [38]. However, there is little evidence for such an assumption in the literature [17]. In all but two studies the degree of clotting was the same or less with LMWH compared to UFH. A low LMWH dosage in the start was thought to be responsible for more clotting with LMWH in two studies [33, 38].

Only 9 of the studies reported that patients treated with both oral anticoagulants and antiplatelet drugs were excluded. This is important information since these drugs interfere with coagulation and haemostasis and may decrease clot formation. It is shown in some studies that the LMWH dose may be reduced in patients treated with warfarin, see Figure 2 [17]. Moreover, aspirin in a dose of 600 mg per day is found to significantly reduce the mean volume loss of the dialyser fibre bundle [39]. However, it remains to be investigated in future studies to what extent the LMWH dose may be lowered in patients treated with these agents.

Safety

Safety was assessed by bleeding complications in 18 and by compression time of the puncture site in 11 studies. In one study there was lower need for erythrocyte concentrates with LMWH as with UFH [2]. Only one study reported significantly more bleeding between HD sessions with LMWH as compared with UFH [30].

Some studies report adding a small dose of LMWH to the priming fluid, but this was found to have no advantage compared to single bolus injection without priming with LMWH-saline [27]. Moreover, the same author reported identical safety and efficacy of administration of LMWH by the arterial and by the venous route.

Doses of LMWH in Dialysis

A) For dalteparin, the earliest studies used a bolus dose at start and a continuous infusion while in recent years the authors more frequently report that a single bolus dose at start is sufficient. For a 4 hours HD session a bolus dose of 70 IU/kg at start is recommended. A single bolus dose of 5000 IU is reported to be sufficient for 5-6 hours dialysis [13].
B) For nadroparin, 50 IU/kg for 4 hours is mentioned as the lowest effective dose. One author recommends 60-80 IU/kg as a bolus dose for 4 hours HD depending on Hct. Others recommend bolus doses of 100 IU/kg for 4 hours sessions. For HD sessions more than 5 hours 80 IU/kg in 2 divided doses is advised, 2/3 at start and 1/3 after 2.5 hours.
C). The recommendation for enoxaparin is a bolus of 0.70 mg/kg for 3-5 hours.
D). For tinzaparin the recommendations vary from 2500 IU to 4250 IU for 4 hours sessions and 5000 IU for 5 hours or more.

(For reviparin and logiparin, see Table 2.)

There is a short report of bemiparin sodium, a new second generation LMWH, in 1426 HD sessions [40]. The dosage was 2500 and 3500 IU in patients <60 and >60 kg, respectively. Bemiparin was as efficient and safe as UFH.

Table 2. Recommended LMWH dosage regimens[a].

LMWH	Studies using i.v. bolus dose + continuous infusion	Dose bolus i.v. + infusion aFXa U + aFXa U/hr or aFXa U/kg + aFXa U/kg/hr (if reported)	Studies using a single bolus dose	Dose single i.v. bolus aFXa U or aFXa U/kg
Dalteparin	9	1750-4000 U+ 750 U/hr or 20-40 U/kg + 8-15 U/kg/hr	7	5000 U or 70 U/kg
Nadroparin	0		7	4000-5000 U[b] or 50-100 U/kg
Enoxaparin	0		3	0.70 mg/kg
Tinzaparin	0		5	2500-5000 U[c]
Reviparin	0		2	85 U/kg
Logiparin	0		1	3000-4000 U

[a] Only recommendations in patients with no bleeding risk is referred to here.
[b] 4000 U for 4 hour dialysis sessions and 5000 for 5 hours.
[c] 2500 U was sufficient for up to 4 hours and 5000 U for 6 hours (Ryan 1991).

Most of the studies report that a plasma anti-FXa activity level of 0.4-0.5 is sufficient to avoid clotting (see Table 1). A significant correlation between plasma anti-FXa level and clinical clotting has been found in clinical studies (see Fig. 2) [17, 21].

In 3 of the studies described in Table 1 hemofiltration (HF) patients were included, and they were successfully treated with dalteparin bolus plus infusion [2, 18, 19]. One study found a single bolus dose of nadroparin (mean 65 IU/kg) equally anticoagulant in HD and in hemodiafiltration (HDF) [26].

LMWHs in Continuous Renal Replacement Therapy

Continuous renal replacement therapies (CRRTs) may be better tolerated than intermittent HD in intensive care unit patients suffering from acute renal failure, multiple organ failure, cardiovascular instability or resistant fluid retention. This treatment modality provides more gradual osmotic shifts and continuous adjustment of intravascular volume. However, these patients are often at high risk of bleeding due to open injuries or surgical wounds, sepsis, consumption coagulopathy, liver failure, clotting factor deficiencies and/or thrombocytopenia. Antithrombin levels are often below normal in patients with sepsis and other causes of systemic inflammation. This contributes to clotting and reduced filter life time despite adequate anticoagulation as measured by activated partial thromboplastin times or anti-FXa activity [41].

There are several methods to prevent clotting in CRRT. Low dose UFH is by some regarded as the standard approach, with or without protamine to produce regional anticoagulation. Other approaches are prostacyclines, LMWHs, citrate anticoagulation, serine-esterase inhibitors and finally no anticoagulation with or without saline flushes. Only LMWHs will be dealt with in this short review.

Although LMWHs have an established role in HD, this does not seem to be the case in CRRT. A Medline search on the use of LMWHs in CRRT resulted in only 5 clinical trials. In 3 of these trials dalteparin was used, one deals with enoxaparin, and in the fifth nadroparin was compared to dalteparin [41-45].

Reeves et al. compared dalteparin bolus 20 U/kg plus infusion 10 U/kg/hr (25 patients) to UFH (22 patients), all treated with predilutional continuous venovenous hemodiafiltration [43]. They found that dalteparin and UFH had similar safety and identical filter life times (46.8 hrs versus 51.7 hrs, respectively), but that dalteparin had increased direct costs compared with UFH. A preceding pilot study had shown that dalteparin 15 U/kg bolus plus 5 U/kg/hr infusion resulted in no bleeding episodes but too short filter life time (22.5 hrs).

In a non-randomized study of Jeffrey et al. 9 patients were treated with continuous venovenous hemodialysis (CVVHD) for a study period of 36 hours [42]. One patient was treated on two occasions. Three patients received high-dose (35 U/kg bolus plus 13 U/kg/hr infusion) and 7 received low-dose dalteparin (8 U/kg and 5 U/kg/hr, respectively). There was minimal clotting with the high-dose regimen, and mean anti-FXa was in the range 0.47-0.75 IU/ml. Mild bleeding episodes occurred in all 3 patients, leading to discontinuation of dalteparin in one. With the low-dose regimen mean anti-FXa was in the range 0.27-0.53 IU/ml and marked thrombus formation occurred, lead-

ing to clotting of the circuit within the study period in 2 patients, at 31 and 34 hours, respectively. One of the 7 patients had a mild bleeding episode.

Singer et al. studied 15 treatments with continuous venovenous hemofiltration (CVVHF) in 10 patients [41]. UFH (8 treatments) was compared to dalteparin (600 U/hr infusion in 7 treatments). Ultrafiltrate anti-FXa levels were insignificant. Nothing is mentioned about pre- or postdilution or filter life time.

Enoxaparin (40 mg bolus followed by boluses 10-40 mg every 6 h) was studied in 7 patients on slow continuous HD [44]. Clotting occurred in 2 cases (anti-FXa 0.14 and 0.18 IU/ml, respectively) and no accidental bleeding occurred.

In a double-blind, randomised, crossover study nadroparin (2050 U bolus plus 328 U/hr infusion) was compared to dalteparin (2000 U bolus plus 320 U/hr) in 32 patients receiving postdilutional CVVHF [45]. Filter life time was the same with the two drugs.

Three of the studies report using a priming procedure with saline containing anticoagulant.

Conclusion

In general LMWHs have potential benefits compared to UFH. In HD most of the knowledge is with use of single bolus doses of dalteparin, nadroparin, enoxaparin and tinzaparin. The treatment appears to be effective and safe. Most reported experience is with dalteparin.

In CRRT reports on efficacy and safety of LMWHs are few but indicate that LMWHs may be used also on this indication.

References

1. Salzman EW, Rosenberg RD, Smith MH, Lindon JN, Favreau L (1980) Effect of heparin and heparin fractions on platelet aggregation. J Clin Invest 65: 64-73
2. Schrader J, Stibbe W, Armstrong VW, Kandt M, Muche R, Kostering H et al. (1988) Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. Kidney Int 33: 890-896
3. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M et al. (1995) Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332: 1330-1335
4. Yamamoto S, Koide M, Matsuo M, Suzuki S, Ohtaka M, Saika S et al. (1996) Heparin-induced thrombocytopenia in hemodialysis patients. Am J Kidney Dis 28: 82-85
5. Section V. Chronic intermittent haemodialysis and prevention of clotting in the extracorporal system. (2002) Nephrol Dial Transplant 17 Suppl 7: 63-71
6. Anastassiades E, Lane DA, Ireland H, Flynn A, Curtis JR (1989) A low molecular weight heparin ("fragmin") for routine hemodialysis: a crossover trial comparing three dose regimens with a standard regimen of commercial unfractionated heparin. Clinical Nephrology 32: 290-296
7. Anastassiades E, Ireland H, Flynn A, Lane DA, Curtis JR (1990) A low-molecular-weight heparin (Kabi 2165, 'Fragmin') in repeated use for haemodialysis: prevention of clotting and prolongation of the venous compression time in comparison with commercial unfractionated heparin. Nephrology Dialysis Transplantation 5: 135-140
8. Apsner R, Horl WH, Sunder-Plassmann G (2001) Dalteparin-induced alopecia in hemodialysis patients: reversal by regional citrate anticoagulation. Blood 97: 2914-2915
9. Borm JJ, Krediet R, Sturk A, ten Cate JW (1986) Heparin versus low molecular weight heparin K 2165 in chronic hemodialysis patients: a randomized crossover study. Haemostasis 16 Suppl 2 :59-68
10. Harenberg J, Haaf B, Dempfle CE, Stehle G, Heene DL (1995) Monitoring of heparins in haemodialysis using an anti-factor-Xa-specific whole-blood clotting assay. Nephrology Dialysis Transplantation 10: 217-222
11. Hofbauer R, Moser D, Frass M, Oberbauer R, Kaye AD, Wagner O et al. (1999) Effect of anticoagulation on blood membrane interactions during hemodialysis. Kidney International 56: 1578-1583
12. Kerr PG, Mattingly S, Lo A, Atkins RC (1994) The adequacy of fragmin as a single bolus dose with reused dialyzers. Artif Organs 18: 416-419
13. Lane DA, Flynn A, Ireland H, Anastassiades E, Curtis JR (1986) On the evaluation of heparin and low molecular weight heparin in haemodialysis for chronic renal failure. Haemostasis 16 Suppl 2 :38-47
14. Leu JG, Chiang SS, Lin SM, Pai JK, Jiang WW (2000) Low molecular weight heparin in hemodialysis patients with a bleeding tendency. Nephron 86: 499-501
15. Ljungberg B, Blomback M, Johnsson H, Lins LE (1987) A single dose of a low molecular weight heparin fragment for anticoagulation during hemodialysis. Clin Nephrol 27: 31-35
16. Ljungberg B, Jacobson SH, Lins LE, Pejler G (1992) Effective anticoagulation by a low molecular weight heparin (Fragmin) in hemodialysis with a highly permeable polysulfone membrane. Clinical Nephrology 38: 97-100
17. Sagedal S, Hartmann A, Sundstrom K, Bjornsen S, Fauchald P, Brosstad F (1999) A single dose of dalteparin effectively prevents clotting during haemodialysis. Nephrol Dial Transplant 14: 1943-1947
18. Schrader J, Valentin R, Tonnis HJ, Hildebrand U, Stibbe W, Armstrong VW et al. (1985) Low molecular weight heparin in hemodialysis and hemofiltration patients. Kidney Int 28: 823-829
19. Schrader J, Kandt M, Zurcher C, Kostering H, Scheler F (1986) Comparison of unfractionated heparin and low molecular weight heparin during long-term use in chronic haemodialysis and haemofiltration patients. Haemostasis 16 Suppl 2: 48-58
20. Suzuki T, Ota K, Naganuma S, Koshikawa S, Hirasawa Y, Nakagawa S et al. (1990) Clinical application of Fragmin (FR-860) in hemodialysis: multicenter cooperative study in Japan. Seminars in Thrombosis & Hemostasis 16 Suppl: 46-54
21. Grau E, Siguenza F, Maduell F, Linares M, Olaso MA, Martinez R et al. (1992) Low molecular weight heparin (CY-216) versus unfractionated heparin in chronic hemodialysis. Nephron 62: 13-17
22. Janssen MJ, Deegens JK, Kapinga TH, Beukhof JR, Huijgens PC, van Loenen AC et al. (1996) Citrate compared to low molecular weight heparin anticoagulation in chronic hemodialysis patients. Kidney International 49: 806-813
23. Lai KN, Wang AY, Ho K, Szeto CC, Li M, Wong LK et al. (1996) Use of low-dose low molecular weight heparin in hemodialysis. American Journal of Kidney Diseases 28: 721-726

24. Lai KN, Ho K, Li M, Szeto CC (1998) Use of single dose low-molecular-weight heparin in long hemodialysis. International Journal of Artificial Organs 21: 196-200
25. Moriniere P, Dieval J, Bayrou B, Roussel B, Renaud H, Fournier A et al. (1989) Low-molecular-weight heparin Fraxiparin in chronic hemodialysis. A dose-finding study. Blood Purification 7: 301-308
26. Stefoni S, Cianciolo G, Donati G, Coli L, La Manna G, Raimondi C et al. (2002) Standard heparin versus low-molecular-weight heparin. A medium-term comparison in hemodialysis. Nephron 92: 589-600
27. Vanuytsel JL, Lins RL, Zachee P, Mattheeussen J, Hosten S, Lens S et al. (1999) Comparison of different routes of administration of nadroparin in hemodialysis. Clin Nephrol 52: 322-325
28. Naumnik B, Borawski J, Mysliwiec M (2003) Different effects of enoxaparin and unfractionated heparin on extrinsic blood coagulation during haemodialysis: a prospective study. Nephrol Dial Transplant 18: 1376-1382
29. Polkinghorne KR, McMahon LP, Becker GJ (2002) Pharmacokinetic studies of dalteparin (Fragmin), enoxaparin (Clexane), and danaparoid sodium (Orgaran) in stable chronic hemodialysis patients. Am J Kidney Dis 40: 990-995
30. Saltissi D, Morgan C, Westhuyzen J, Healy H (1999) Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation. Nephrol Dial Transplant 14: 2698-2703
31. Beijering RJ, ten Cate H, Stevens P, Vanholder R, Van Dorp WT, van Olden RW et al. (2003) Randomised long-term comparison of tinzaparin and dalteparin in haemodialysis. Clin Drug Invest 23: 85-97
32. Egfjord M, Rosenlund L, Hedegaard B, Buchardt HL, Stengel C, Gardar P et al. (1998) Dose titration study of tinzaparin, a low molecular weight heparin, in patients on chronic hemodialysis. Artificial Organs 22: 633-637
33. Lord H, Jean N, Dumont M, Kassis J, Leblanc M (2002) Comparison between tinzaparin and standard heparin for chronic hemodialysis in a Canadian center. American Journal of Nephrology 22: 58-66
34. Ryan KE, Lane DA, Flynn A, Shepperd J, Ireland HA, Curtis JR (1991) Dose finding study of a low molecular weight heparin, Innohep, in haemodialysis. Thromb Haemost 66: 277-282
35. Simpson HK, Baird J, Allison M, Briggs JD, Rowe PA, Welsh M et al. (1996) Long-term use of the low molecular weight heparin tinzaparin in haemodialysis. Haemostasis 26: 90-97
36. Baumelou A, Singlas E, Petitclerc T, Desmichels D, Jacobs C, Soria J (1994) Pharmacokinetics of a low molecular weight heparin (reviparine) in hemodialyzed patients. Nephron 68: 202-206
37. Reach I, Luong N, Chastang C, Chakroun M, Mirshahi S, Mirshahi MC et al. (2001) Dose effect relationship of reviparin in chronic hemodialysis: a crossover study versus nadroparin. Artificial Organs 25: 591-595
38. Koutsikos D, Fourtounas C, Kapetanaki A, Dalamanga A, Tzanatos H, Agroyannis B et al. (1996) A cross-over study of a new low molecular weight heparin (Logiparin) in hemodialysis. International Journal of Artificial Organs 19: 467-471
39. Stewart JH, Farrell PC, Dixon M (1975) Reduction of platelet/fibrin deposition in haemodialysers by aspirin administration. Aust N Z J Med 5: 117-122
40. Planes A (2003) Review of bemiparin sodium--a new second-generation low molecular weight heparin and its applications in venous thromboembolism. Expert Opin Pharmacother 4: 1551-1561
41. Singer M, McNally T, Screaton G, Mackie I, Machin S, Cohen SL (1994) Heparin clearance during continuous veno-venous haemofiltration. Intensive Care Medicine 20: 212-215
42. Jeffrey RF, Khan AA, Douglas JT, Will EJ, Davison AM (1993) Anticoagulation with low molecular weight heparin (Fragmin) during continuous hemodialysis in the intensive care unit. Artif Organs 17: 717-720
43. Reeves JH, Cumming AR, Gallagher L, O'Brien JL, Santamaria JD (1999) A controlled trial of low-molecular-weight heparin (dalteparin) versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. Crit Care Med 27: 2224-2228
44. Wynckel A, Bernieh B, Toupance O, N'Guyen PH, Wong T, Lavaud S et al. (1991) Guidelines to the use of enoxaparin in slow continuous hemodialysis. Contributions to Nephrology 93: 221-224
45. de Pont AC, Oudemans-van Straaten HM, Roozendaal KJ, Zandstra DF (2000) Nadroparin versus dalteparin anticoagulation in high-volume, continuous venovenous hemofiltration: a double-blind, randomized, crossover study. Critical Care Medicine 28: 421-425

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