Saudi J Kidney Dis Transpl 2010;21(3):466-470

Saudi Journal of Kidney Diseases and Transplantation

Original Article

Effect of Vitamin E Coated Dialyzers on Anticoagulation Requirement in Hemodialyzed Children

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ABSTRACT. As hemodialysis (HD) requires extra corporal blood flow and the need for anticoagulation, we evaluated the effect of vitamin E coated membranes (VIE) on the requirement of low molecular weight heparin (LMWH) in pediatric HD patients. Patients and methods: seven children and adolescents on regular hemodialysis were started on VIE and their LMWH dose was decreased every week. In order to monitor the requirement of LMWH we used a coagulation score to evaluate coagulation in the dialyzer, air trap and blood line. Other classical parameters (hemoglobin, erythropoietin dose, inflammatory markers) were monitored weekly while the patients were on VIE dialyzers. LMWH dose during the 1st week was 110 IU/kg ± 18 (defined as 100%), in the 2nd week the dose was 77 IU/kg ± 12 (70%), in the 3rd week the dose was 33 IU/kg ± 5 (30%), and in the 4th week anticoagulation could be stopped in one patient, in the other six patients further decrease was impossible given the increase of the clotting score. There was no increase in clotting score during week one and two. During week three (while on 30% of the initial LMWH dose) six patients showed mild to moderate clotting phenomena: mild coagulation phenomena in three patients and moderate clotting phenomena in three others. One patient did not show any clotting phenomena in week three and LMWH was totally stopped. In conclusion, use of VIE dialyzers may help to reduce the requirement of anticoagulation in pediatric HD patients reducing bleeding problems and simplify hemostasis after HD sessions.

Introduction

Hemodialysis (HD) requires extracorporeal blood flow and anticoagulants. Dialyzer clotting is a common factor underlying poor dialysis performance and may be responsible for difficulties in anemia management and excessive EPO requirement.[1] In order to prevent clotting phenomena, anticoagulation is often increased exposing the patient to higher risk of hemorrhage and prolonged bleeding times of the arteriovenous fistula.

The plasma half life time of low molecular weight heparin (LMWH) is dependent on renal clearance. Thus, patients with renal failure are

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potentially at risk for bleeding as a result of impaired LMWH clearance and prolonged anticoagulant effects.[2] Despite the general avoidance of LMWH in HD patients, they are routinely used to prevent thrombosis of the extracorporeal dialysis circuit.[3,4]

LMWH are not removed from the plasma during hemodialysis[2] or continuous veno-venous hemofiltration. Thus, LMWH can accumulate during dialysis sessions and increase the risk for bleeding. It has been shown that the risk for hemorrhage in the HD population was increased by 10-fold.[5]

Strategies to decrease anticoagulation requirement during HD sessions are therefore warrented. VitabranE (VIE) is a polysulfone dialyzer coated with vitamin E alpha-tocopherol. VIE consist of a polysulfone membrane grafted with liposoluble vitamin E on the blood side allowing direct free radical scavenging at the membrane site.[6] It has been suggested that vitamin E coated membranes may have potentially beneficial effects such as reduced microinflammation and oxidative stress[7] as well as improved stabilization of the erythrocyte membrane.[7] Recently it has been suggested that vitamin E coated membranes may decrease anticoagulation requirement during dialysis session.[9,3,10]

Since no studies in children have been performed so far to evaluate the effect of VIE on anticoagulation use or anemia, we undertook this pilot study in seven children undergoing HD.

Patients and Methods

We included in this prospective study all patients from one single pediatric nephrology department who were on chronic hemodialysis for three 4-hour sessions per week for more than six months. All patients underwent HD sessions with the use of high flux dialyzers adapted to patients' body surface area. We analyzed hemoglobin levels (Hb), C-reactive protein (CRP), procalcitonin (PCT), IL-6, as well as LMWH and EPO doses (darbepoetin alpha) immediately before, during, and after the switch to VIE dialyzer. All patients were dialyzed initially using high permeability membranes (FX 100, Fresenius, Germany). Dialysis machine in all patients was Gambro AK200S.

LMWH dose required for hemodialysis session before the use of vitamin E coated dialyzers was defined as 100%. During the first week all patients were switched to vitamin E coated membranes (VIE dialyzers, Asahi Kuraray Kasei Medical, Japan) with an equivalent membrane surface and maintained on the same dose of LMWH. On the second week the dose of LMWH was decreased to 70% of the initial dose without changes of other HD parameters. On the third week the LMWH dose was decreased to 30% of the initial dose and totally stopped on the fourth week. In case of moderate clotting phenomena no further decrease of LMWH dose was performed. In case of severe clotting phenomena the study was interrupted and the initial LMWH dose used for the next session.

Dialyzer clotting score

During each HD session, blood lines, air traps and dialyzers were analyzed. We used a scoring system for semiquantitative description of the clotting activation in the dialyzer from 1 to 4 after each HD session: 1-no blood trace, clear color, 2-rare blood traces, 3-moderate blood traces, 4-severe blood coagulation. The presence of blood clots in air traps and blood lines was analyzed. Mild clotting phenomena were defined as dialyzer score ≤ 3, without blood clots in air trap or blood lines.

Presence of small blood clots in air trap or blood lines or dialyzer score > 3 were considered as moderate, and bigger blood clots in air trap or precocious interruption of HD session caused by clotting problems as severe clotting phenomena.

Coagulation parameter analysis

All patients were analyzed for coagulation parameters (protein C, protein S, antithrombin III, mutation of factor V, mutation of factor II, fibrinogen, MTHFR mutations).

History of thromboembolic events was recorded for each patient.

Table 1. Patient clinical parameters

No.	Age (years)	Sex	Initial pathology	Dialyzer Type I	Dialyzer Type II	Risk factors
1	17	M	RD	FX100	VIE-21	MTHFR, heterozygote
2	15	M	PUV	FX80	VIE-18	Fact. V heterozygote
3	12	M	aHUS	FX80	VIE-18	NO
4	16	F	LN	FX100	VIE-21	Elevated Protein C
5	18	M	SRNS	FX100	VIE-21	NO
6	17	M	SRNS	FX100	VIE-21	NO
7	17	M	IgA nephropathy	FX100	VIE-21	MTHFR, heterozygote

Patients' characteristics, RD: renal dysplasia; PUV: posterior urethral valve; aHUS: atypical hemolytic and uremic Syndrome, LN: lupus nephropathy; MTHFR: Methelentetrahydrofolate reductase, SRNS: Steroid resistant nephrotic syndrome

Statistical Analysis

Statistical analysis was performed using sigma-stat (version 3.5). Data were summarized as mean ± standard error of the mean (SEM) for normally distributed data and as median and range for data that were not normally distributed. *P*-values < 0.05 were considered statistically significant.

Results

Seven children on regular HD were included. Median patient age was 15 years (range 12-17); LMWH was used for anticoagulation during HD in all patients. Patient characteristics, including prothrombotic factors and main dialysis parameters are summarized in Table 1. Dialyzer clotting scores of all patients over the study period are given in Table 2. Before starting the patients on VIE and during the 1st week of VIE, mean LMWH dose was 110 IU/kg ± 18 (100%), on the 2nd week 77 IU/kg ± 12 (70%); on the 3rd week 33 IU/kg ± 5 (30%), and on the 4th week the anticoagulation was stopped in one patient. In the other six patients further decrease was not performed as increased clotting phenomena were noted (Table 2). Therefore, in these six patients week four was conducted with the same anticoagulation as week three. No patient showed severe interdialytic clotting phenomena

There was no increase in clotting score during week one and two. During week three (while on 30% of the initial LMWH dose) six patients showed mild to moderate clotting phenomena: mild coagulation phenomena in three patients and moderate clotting phenomena in three others. One patient did not show any clotting phenomena in week three and LMWH was totally stopped. In week four he was dialyzed without LMWH, but filter clotting score increased from one to three in all three sessions during week four whereas no other clotting phenomenon was noticed in this patient.

Hemoglobin levels before (13.5 g/dL ± 0.7),

Table 2. Dialyzer clotting scores in the successive weeks

Patient No.	Week 1 (100%)			Week 2 (70%)			Week 3 (30%)			Week 4 (0%)		
	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
1	2	2	2	2	2	2	1*	3*	3*			
2	2	2	2	2	2	1	3*	1*	4*			
3	1	2	2	2	1	1	1	3	3			
4	1	1	2	2	1	2	1*	1*	1*			
5	2	2	1	1	2	1	1	1	3			
6	1	1	1	1	1	1	1	2	3			
7	1	1	1	1	1	1	1	1	1	1	2*	3*

Dialyzer Clotting-Score in week 1 to 4: 1-no blood trace, clear color, 2-rare blood traces, 3-moderate blood traces, 4-severe blood coagulation. In patient 1 to 6 no further decrease of LMWH was performed because of increased clotting phenomena. *small blood clots in air trap

during (14 g/dL ± 0.8) and one month after (12 g/dL ± 2) the use of VIE, were not significantly different. EPO dose was (0.5 μg/kg ± 0.3) before, (0.4 μg/g ± 0.2) during, and (0.38 μg/kg ± 0.19) one month after the use of VIE dialyzers. CRP, PCT, and IL-6 remained in the low normal range during the whole study for all patients.

Among the three patients with moderate clotting increase during the decrease of the LMWH dose, one patient had a heterozygote mutation of the MTHFR. Another one had a low protein C level. The 3rd patient had atypical hemolytic uremic syndrome secondary to Factor H deficiency, and medical history of repeated thrombosis in his AVF and central venous catheter.

Discussion

The results of our study suggest that the use of VIE dialyzers may allow a decrease of anticoagulation during the HD session in some children and adolecents on chronic HD. In three of the seven patients a decrease by 70% of the initial LMWH dose led to significant coagulation in the hemodialysis circuit, but these patients had underlying disorders related to a higher risk for blood clotting.

In patients without intrinsic risk factors for coagulation, we decreased LMWH dose by 70% before experiencing a certain degree of coagulation in the dialyzer. Those with risk for coagulation needed a higher dose of LMWH, but we were able to decrease the dose by 30% before starting to experience coagulation in the dialyzer. Further, it is known that in patients with prothrombotic risk factors LMWH requirement is generally higher than in normal subjects.

A controlled study design would have been of interest; unfortunately in a pediatric hemodialysis center, patient number is relatively small. Further, differences in age, body mass index, and underlying disorders make a matched control group very difficult. Moreover, all hemodialyzed children are on a transplantation waiting list and the period on HD before transplantation is relatively short compared to adults, making a cross over study very difficult.

Studies on adult patients have demonstrated that the use of vitamin E coated dialyzers helps to reduce clotting problems in high risk patients.[13] These authors have shown that thrombembolic events can be reduced in high risk patients and anticoagulation can be decreased in patients without prothrombotic risk factors.

One important goal in the treatment of children and adolescents with ESRD is that social life remains as 'normal' as possible. Social activities and sport contribute to psychological stability and well-being. Physical activity exposes hemodialysis patients to potential trauma and hemorrhage.[14] However, hemorrhage in HD patients on LMWH remains relatively rare.[15] Nevertheless, a risk reduction for hemorrhage may increase physical activity, which is considered as an important protective factor for cardiovascular disease.

Others have reported a beneficial effect of vitamin E coated membranes on intra- and interdialytic complications.[16] In our study, two of the seven included patients have reported less thirst and less fatigue after the dialysis session. Due to the small sample size we cannot draw confident conclusions and a lager trial in children may help in supporting our conclusions. Patients' hemoglobin levels did not change significantly. This result is difficult to interpret due to the very short period on VIE dialyzers. The VIE dialyzer consists of a basis in polysulfone (known for its excellent biocompatibility) associated to polyvinylpyrrolidone to increase the diffusive properties and a vitamin E coating with antioxidant properties. Oxygen free radicals may play a pathogenic role in some hemodialysis related complications.[16] The VIE dialyzer, in addition to anti-oxidant properties, has improved biocompatibility characteristics due to its design aimed at limiting blood-membrane interaction. In our pediatric HD patients inflammation markers were low on standard polysulfone dialyzers and remained low on VIEs.[17] Therefore, reduced inflammation cannot be assumed to be responsible for the noticed benefits.[18] Another hypothesis could be that current inflammation markers, such as CRP, PCT and IL-6 are not sensitive

enough to monitor inflammation in pediatric HD patients.

Both coagulation within the circuit and hemorrhage can result in HD related anemia.[19] In adults a positive effect of VIE on hemoglobin levels was shown previously.[1]

We did not find any effect of VIE dialyzers on anemia or EPO requirement, but our observation period was too short to interpret such a negative result. Thus, longer prospective controlled studies with more subtle inflammation markers on a larger patient number are warranted to confirm our results.

In conclusion, the use of VIE dialyzers may help to reduce the requirement of anticoagulation in pediatric HD patients. This might reduce bleeding problems and simplify hemostasis after HD sessions.

References

1. Cruz DN, De Cal M, Garzotto F, et al. Effect of vitamin E-coated dialysis membranes on anemia in patients with chronic kidney disease: an Italian multicenter study. Int J Artif Organs 2008;31:545-52.
2. Lim W, Cook DJ, Crowther MA. Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials. J Am Soc Nephrol 2004;15:3192-206.
3. Mandolfo S, Bucci R, Imbasciati E. Vitamin E-coated membrane dialyzer and beta2-microglobulin removal. Artif Organs 2003;27: 1123-7.
4. Schneiter S, Huynh-Do U, Heizmann M. Bleeding complication due to accumulation of low-molecular-weight heparin in a patient with renal insufficiency. Praxis (Bern 1994) 2007; 96:733-7.
5. Davenport A. Practical guidance for dialyzing a hemodialysis patient following acute brain injury. Hemodial Int 2008;12:307-12.
6. Satoh M, Yamasaki Y, Nagake Y, et al. Oxidative stress is reduced by the long-term use of vitamin E-coated dialysis filters. Kidney Int 2001;59:1943-50.
7. Morimoto H, Nakao K, Fukuoka K, et al. Long-term use of vitamin E-coated polysulfone membrane reduces oxidative stress markers in haemodialysis patients. Nephrol Dial Transplant 2005;20:2775-82.
8. Uzum A, Toprak O, Gumustas MK, et al. Effect of vitamin E therapy on oxidative stress and erythrocyte osmotic fragility in patients on peritoneal dialysis and hemodialysis. J Nephrol 2006;19:739-45.
9. Cruz DN, de Cal M, Ronco C. Oxidative stress and anemia in chronic hemodialysis: the promise of bioreactive membranes. Contrib Nephrol 2008;161:89-98.
10. Girndt M, Lengler S, Kaul H, et al. Prospective crossover trial of the influence of vitamin E-coated dialyzer membranes on T-cell activation and cytokine induction. Am J Kidney Dis 2000;35:95-104.
11. Usalan C, Erdem Y, Altun B, et al. Protein Z levels in haemodialysis patients. Int Urol Nephrol 1999;31:541-5.
12. Nampoory MR, Das KC, Johny KV, et al. Hyper coagulability: A serious problem in patients with ESRD on maintenance hemodialysis, and its correction after kidney transplantation. Am J Kidney Dis 2003;42:797-805.
13. Huraib S, Tanimu D, Shaheen F, et al. Effect of vitamin-E-modified dialysers on dialyser clotting, erythropoietin and heparin dosage: a comparative crossover study. Am J Nephrol 2000;20:364-8.
14. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost 2004;30:579-89.
15. Gouin-Thibault I, Pautas E, Siguret V. Safety profile of different low-molecular weight heparins used at therapeutic dose. Drug Saf 2005; 28:333-49.
16. Tanimu D, Huraib S, Shaheen FA, et al. The Effect of Vitamin E-Modified Dialyzers on Acute Intra-dialytic Symptoms: A Comparative Crossover Study. Saudi J Kidney Dis Transpl 2000;11:543-7.
17. Sasaki M. Development of vitamin E-modified polysulfone membrane dialyzers. J Artif Organs 2006;9:50-60.
18. Calo LA, Naso A, Pagnin E, et al. Vitamin E-coated dialyzers reduce oxidative stress related proteins and markers in hemodialysis-a molecular biological approach. Clin Nephrol 2004;62:355-61.
19. Zachee P, Vermylen J, Boogaerts MA. Hematologic aspects of end-stage renal failure. Ann Hematol 1994;69:33-40.