CASE STUDY

Effectiveness and Safety of Single Bolus Heparin as Anticoagulant in Hemodialysis

Ahmad F Alkhafaji*[1], Sattar J Saadi[1], Hayder S Gatea[2], Jawad I Rasheed[1]

[1]*Medical City Teaching Hospital, Baghdad, Iraq*
[2]*Authority of Health and Medical Education, Karbala, Iraq*

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ABSTRACT

Anticoagulation in hemodialysis is targeted to prevent the activation of coagulation during the procedure. Most agents inhibit the plasmatic coagulation cascade. Still commonly used is unfractionated heparin, followed by low-molecular-weight heparin preparations with distinct advantages. Patency of the circuit is an important prerequisite for optimal hemodialysis quality. Aim of this study was to evaluate the effectiveness and safety of anticoagulant protocol in single hemodialysis center.

Subjects and Method: This prospective cross-sectional study was conducted at Baghdad Teaching Hospital in 2018. Forty patients on HD receiving UFH (5000 IU) as a single bolus dose were included in this study. Coagulation parameter represented by plasma PTT was assessed pre and post administration of bolus dose of 5000 IU heparin on hourly interval. The results of aPTT assessment with current study compared to that of standard method.

Results: The PTT was changed from 29.05 ± 4.3 SD on pre-dialysis to 92.9 ± 12.2, 64.6 ± 15.2, 35.5 ± 8.4 SD at end of first, 2nd and 3rd hour respectively, (p=0.001).The a PTT was significantly higher than standard method on first(92.9 vs.72.69) but lower than standard method on second hour(64.65 vs. 72.69) and 3rd hour(35.5 vs.43.6.1) of administration heparin. The venous and arterial pressure near to normal range but prefilter pressure was significantly increased with time even it remains within normal range.

Conclusion: Our findings suggest that using heparin in bolus dose is effective but unsafe at first hour of administration less effectiveness was reported at 3rd hour of use.

Keywords: Coagulation, Hemodialysis, Heparin.

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INTRODUCTION

The contact between blood and various plastic surfaces within the extracorporeal circuit during hemodialysis process initiates platelet adherence, activation of the intrinsic clotting pathway, and thrombosis. The resulting thrombus formation may be significant enough to cause occlusion and malfunction of the extracorporeal circulation.[1] The clotting is promoted by slow blood flows, High Hb, High UF rate. Intradialytic blood transfusion and parenteral nutrition containing lipid.[2] Most dialysis sessions require anticoagulation, usually with unfractionated heparin (UFH), low-MW heparin (LMWH), epoprostenol, and regional anticoagulation with citrate.[3] A dialysate using low-dose citric acid instead of acetic acid as the acidifying agent may allow a heparin-free or reduced heparin dose dialysis4 where routinely used it is a reliable and effective mean of anticoagulation. Direct thrombin inhibitors, primarily argatroban,[5,6] are useful for patients with HIT, or where heparin is ineffective because of inherited or acquired Antithrombin deficiency, regional citrate dialysis can be use.[7,8]

Bolus injection of heparin followed by infusion or repeated bolus injections, after priming circuit with heparinized saline. Some degree of heparin adsorption to the dialyzer and circuit occurs. There are no good studies demonstrating the best method, and there are a wide range of methods in use in practice.[2]

Infusion Method

Initial bolus usually 2000 U (25 U/kg).Continuous heparin infusion into arterial line at 500–2000 U/h, monitored hourly, more frequently in new patient, adjust infusion rate to clotting time. Stop heparin 60min before end of dialysis.

**Author for Correspondence: alkafagiahmed8@gmail.com*

Bolus Method

Two or three doses of hepain required Initial bolus usually 4000 U but sometimes lower, second 1000-2000 U when PTT or ACT reach to less than baseline level + 50% monitor every hour. time to stop heparin usually 1-hours before the end of dialysis.

Tight (or minimal) Heparin

For patients at moderate risk of bleeding, target ACT or APTT is baseline +40% Achieved by 30 minutes bolus injections of 500 U,or preferably, constant infusion of 250–2000 U/h (usually 600 u\h) after reduced (or no) initial bolus (750 U; check ACT or PTT after 3 min). Monitor every 30 minutes.

Activated partial thromboplastin time (APTT), Activated clotting time (ACT) common Clotting tests used to monitor heparin therapy. long term use of heparin increase risk of osteoporosis,[9] and hypertrigiycerdemia and low HDL cholesterol[10] two random control trials in dialysis patient that failed to show a mortality benefit of statin therapy,[11,12] and hyperkalemia by an effect of heparin on aldosterone[13]

Pressures in Hemodialysis Machine[1]

Inflow pre-pump (p1) pressure (Arterial pressure); usually, the inflow pressure is -80 to -200 mmHg. If the access is not providing sufficient blood to the pump the suction proximal to the blood pump will increase, as in hypotension, small arterial needle, inflow thrombosis, kinking of the arterial line.Post pump, prefilter (p2) pressure; normal range (100-300). The pressure reading in this segment is always positive (above atmospheric). The pressure at the post-pump monitor is normally quite high and depends on the blood flow rate, blood viscosity, and downstream resistance at the dialyzer and beyond. A sudden rise in the P2 is often a sign of impeding clotting of the blood line and\or dialyzer. Outflow, venous (p3) pressure monitor. Usually, the pressure here is +50 to +250 mm Hg, depending on needle size, blood flow rate and hematocrit. And patency of needle or venous limb of vascular access.

Aims of study were to evaluate the effectiveness and safety of single bolus dose of unfractionated heparin in hemodialysis.

Patients and Methods

A prospective cross-sectional study was conducted at Baghdad Teaching Hospital (dialysis center). A convenient sample of 40 patients (55% male, 45% females) with ESRD on regular hemodialysis program was included in this study, where ten patients were enrolled daily for four successive days (6–9 May.2018) from dialysis center. 2 mL of blood was collected from each patient in plastic tubes for each sample that contain trisodium citrate pre and throughout dialysis session for assessment of Activated partial thromboplastin time (Normal range- 24–36).samples of blood were taken according to following schedule as the dialysis session usually continue for four hours :-Liver function test, PTT, platelet count was done for all participants before dialysis session(before heparin)

first sample;- one hour post administration of heparin. second sample; - Two hours post administration of heparin. third sample;- after 3 hours from taken heparin. The samples was taken from arterial line of machine. In addition to laboratory findings of PTT level, the arterial, venous and pre-filter pressure was recorded from machine, the patients were observed for any episode of bleeding or status of thrombosis. The socio-demographic characteristics of the patients also reported. Anticoagulant protocol used as 1cc (5000IU) of unfractionated heparin single bolus dose before starting hemodialysis.

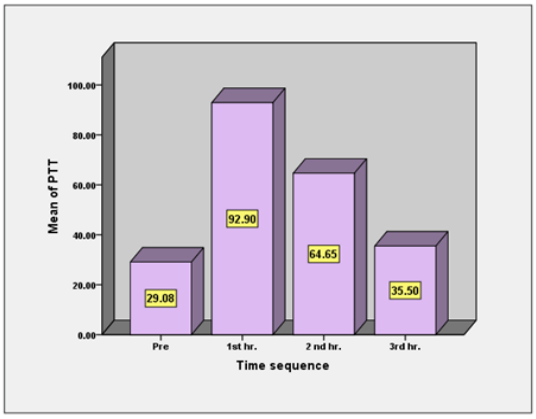

Figure 1: Mean value of PTT with using of bullous dose of 5000 IU of heparin for different points of assessment.

Inclusion Criteria

Any patient older than 18 year's old, Wight range (50–90) Kg, Irrespective the gender, on hemodialysis program, 4hour length of session. Use low flux filter, ultra-filtration rate (5–10) mL/kg/hours.

Exclusion Criteria

Any patient with abnormal Liver function test (include viral hepatitis). Abnormal PT, PTT, platelet below 100,000, history of recent bleeding or coagulopathy, patient on anticoagulants.

Statistical Analysis

SPSS version 23 was used for data entry and analysis. Mean and standard deviation used to represent the numerical data while frequency and percentage for categorical data. Independent student, paired sample t test, Pearson correlation and chi-square (fisher exact when not applicable) tests were used to confirm significance. $p \leq 0.05$ considered significant.

RESULTS

The findings of current study revealed that 55% of studied group was male and 45% was female as well as the mean age of male and female patients did not differ significantly (p=0.8) as seen in Table 1

The results with PTT level assessment revealed there was significant difference in mean value of PTT level pre and consecutive assessment for three hours on one hour interval. On further analysis with LSD test for multiple comparison of mean value of PTT level according to time of assessment, the significant difference also documented as seen in Table 2 and 3 and Figure 1

Our data indicated that the mean value of PTT significantly higher ($p = 0.001$) with current schedule (92.9 ± 22.2 sd) than

Table 1: Mean value of age according to gender of patients.

	Gender				
	Male		*Female*		*p-value*
	Mean	*Standard deviation*	*Mean*	*Standard deviation*	
Age	56.3	12.2	55.7	12.3	0.8

Table 2: Mean value of PTT pre, 1st, 2nd and 3rd hours post using of 5000 IU of heparin.

PPT level							
				95% Confidence Interval for Mean			
	N	*Mean*	*Std. deviation*	*Lower bound*	*Upper bound*	*Minimum*	*p-value*
pre	40	29.08	4.370	27.68	30.47	22	0.001
1st hour	40	92.90	22.221	85.79	100.01	39	
2nd hour	40	64.65	15.526	59.68	69.62	39	
3rd hour	40	35.50	8.406	32.81	38.19	26	

Table 3: Multiple comparison of PTT level with time sequence.

Multiple comparisons					
Dependent variable: PPT level					
LSD					
(I) Time sequence	*(J) Time sequence*	*Mean difference (I-J)*	*p-value*	*95% Confidence interval*	
				Lower bound	*Upper bound*
pre	1st hour	-63.825*	0.001	-70.17	-57.48
	2nd hour	-35.575*	0.001	-41.92	-29.23
	3rd hour	-6.425*	0.04	-12.77	-.08
1st hour	pre	63.825*	0.001	57.48	70.17
	2nd hour	28.250*	0.001	21.91	34.59
	3rd hour	57.400*	0.001	51.06	63.74
2nd hour	pre	35.575*	0.001	29.23	41.92
	1st hour	-28.250*	0.001	-34.59	-21.91
	3rd hour	29.150*	0.001	22.81	35.49
3rd hour	pre	6.425*	0.04	.08	12.77
	1st hour	-57.400*	0.001	-63.74	-51.06
	2nd hour	-29.150*	0.001	-35.49	-22.81

Table 4: Difference in mean value of PTT between current schedule and standard method at 3 points of assessment.

	Groups	*Mean*	*Std. deviation*	*p-value*
1st hour	Our regime	92.90	22.2	0.001
	Standered	72.69	7.8	
2nd hour	Our regime	64.65	15.5	0.001
	Standered	72.69	7.8	
3rd hour	Our regime	35.50	8.4	0.009
	Standered	43.61	6.1	

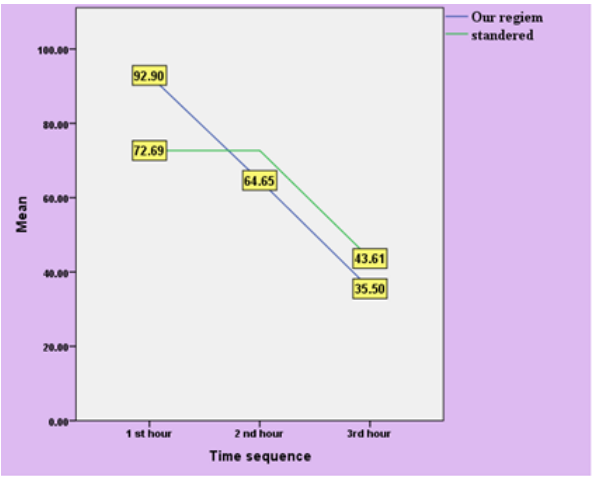

Figure 2: Difference in mean value of PTT between current schedule and standard method at 3 points of assessment.

standard method (72.69 ± 7.8 sd) at last first hour of post using the bolus dose of 5000 IU of heparin. The results demonstrated that the prolongation in PTT level was less at last second hour of using the 5000 IU of heparin (mean=64.65 ± 15.5 sd) and it was significantly less than the mean value of PTT that obtained with standard method of heparin use. The mean value of PTT was significantly lower ($p = 0.009$) than the level that expected

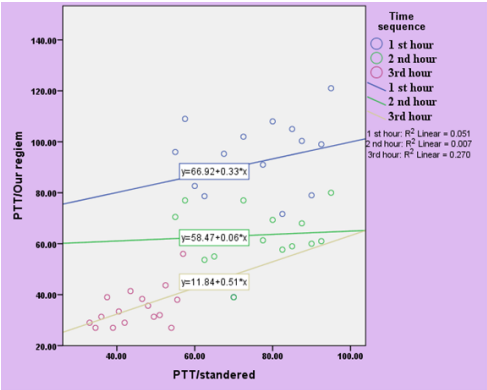

Figure 3: Correlation between PTT value of current schedule and standard schedule at 3 points of assessment.

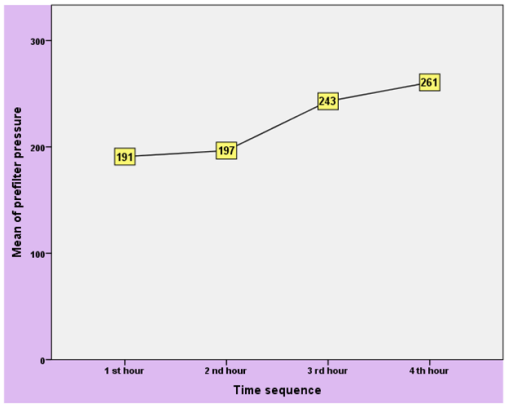

Figure 4: Mean of pre-filter pressure with time sequence of dialysis.

to obtain with standard method (35.5, 43.61), respectively at last third hour, as displaced in Table 4 and Figure 2.

The findings of current study revealed there was weak insignificant direct correlation between the PTT level of our regime and standard method at the first hour of heparin use which calculated on the base of 250% as maximum increases of PTT value in comparison to predialysis value(accept range 200–250%) from aPTT before dialysis. The weak direct correlation between value of PTT of our regime and standered method also reported at 2nd hours of heparin use (accept range the same in first hour). At end of 3rd hours(last hour) the correlation become direct as the PTT level was decrease when correlated with expected value of PTT with standered method that calculated on the base of 150% as minimum increasing of predialysis value of PTT (accept range 150–200%) in last of third hour, as seen in Figure 3

The pre-filter pressure significantly(p=0.03) increased from first hour to fourth hour(end of 4th hour) of dialysis as the mean value of pre-filter pressure was changed from 191 mmHg at first hour to 261 mmHg at the end of dialysis as seen in Figure 4.

The mean value of venous pressure was ranged from 70–230 while arterial pressure ranged from -40 to -310 these value, its near normal range, no significant increases or decreases with time or with changing of a PTT.

DISCUSSION

The using of unfractionated heparin to prevent clotting of the extracorporeal circuit was considered one of the key advances that result in rapid development of hemodialysis process[14] and it remains as main important step in HD practice. However, the anticoagulant using during hemodialysis for patients at high risk of bleeding remains a frequently encountered problem.[15]

The aPTT must remain in range (200–250%) at the beginning until last hour, where the range (150–200%) , Above the upper range increase risk of bleeding, below than lower range increase risk of extracorporeal thrombosis.[1]

There are different protocol of given heparin during hemodialysis process as well as the dose of unfractionated heparin or low molecular weight heparin administered during hemodialysis widely varied. The first protocol that commonly used consists of a standard dose of heparin given as a bolus at the beginning of the dialysis process, with a mid-treatment dose to maintain suitable anticoagulation. The second protocol is that heparin given as an initial bolus followed by a constant fixed infusion.[16]

In current study we observed that the aPTT prolonged to level higher than 250% of pre-dialysis level at first hour of administration the bolus dose of heparin and the obtained level was significantly higher than that must obtained by standard protocols and such prolongation may increases the probability of bleeding at this time of dialysis, in addition the aPTT level was decreased to unaccepted level at last hour of dialysis which may increases the rate of thrombosis at the end of dialysis process. These findings reflect the effectiveness of such bolus dose on first hour of use but the safety cannot be assured. Although bleeding is considered the most common complication with using of heparin, we did not noticed any association between heparin use and dangerous bleeding such as gastrointestinal or intracranial bleeding .our finding are in consistent with results of Wasse *et al.*[17] who found that the using of anticoagulant medication for prevention of thrombosis during the HD was not associated with increased risk of gastrointestinal bleeding.

To our knowledge and it is important to mention that there was no similar studies on national or international level that evaluated the effectiveness and safety of single bolus dose of heparin in hemodialysis process but most was compared the intermittent and infusion protocol in different dosage. A number of studies evaluated the reduced-dose of UFH (LD 20 units/kg followed by MD 1000–1500 units/hour) to increase the ACT by 20%–50%; results suggested similar dialysis adequacy of intermittent protocol to infusion protocol with unchanged rates of extracorporeal thrombosis using several different dialyzer membranes.[18]

Author Fischer KG,19 was reported that the UFH has a narrow therapeutic window of adequate anticoagulation with all doses and protocols therefor the periodic laboratory testing (aPTT, ACT) to monitor and assess its effect is required. According to European best practice guidelines for hemodialysis (part 1), 20 the half-life of UFH life between 0.5 and 2.0 hours in patients receiving dialysis and that half-life can be modified by nonspecific binding to the leukocytes, endothelium and plasma proteins. This short half-life of heparin may explain

our finding at third hour of dialysis as the obtained level was lower than what was supposed to have by others protocols. UFH is highly charged and therefore nonspecific binding to plastic tubing and dialyzer membrane surfaces can occur altering its pharmacokinetics. In alternative method of heparin given, the maintenance infusion is stopped 60 min before the end of treatment to reduce bleeding times from fistula needle sites at end of dialysis.

Depending on findings of many studies, Roy A, Kalra V21 were concluded, if the bleeding risk is extremely high (e.g., in patients at risk for intracranial bleeding, pericarditis, recent surgery), maintenance heparin is completely avoided. Heparin-free dialysis can use, Alternative approaches include tight heparin method where a PTTr of 1.5–2.0, from beginning until end of third hour of dialysis.

As we said in the result, venous and arterial pressure recording in this study, because increase in these pressures may as a sign of thrombosis. venous pressure remain within normal range (70–230).and arterial pressure (-40 to -310) near normal, really unrelated to time of dialysis some patient started high venous or arterial pressure and remain high, other started low and remain low or then increase despite high aPTT, that's mean there is other factors affect to these pressures as blood pressure of patient, needle size, rate of Ultra filtration, hemoglobin level and many other factors. We need another study to evaluate these pressure and main cause of changing during dialysis.

In our study, we noticed that the pre-filter pressure changed from 191mmHg at pre-dialysis to 261 mmHg at fourth hour of dialysis process and this finding showed it wasn't raise beyond the normal range (100–300) mmHg. The finding showed it was raised slightly within the first hours of dialysis process but much rising was reported at the last hours of dialysis. The most accepted explanation for this rising, is the affection of dialyzer filters by small clots that developed throughout the dialysis process or accumulation of dialysis west product ,or increase UF.increase prefilter pressure associated with decrease apTT in third hour and continue raise until last 4th hours may caused by small clots that developed through the dialysis process, that's cause resistance blood flow, and increase prefilter pressure.

CONCLUSIONS

- Effectiveness of single bolus dose of heparin cannot reach international standard of anticoagulant in hemodialysis.
- Single bolus dose protocol may unsafe, because increase risk of bleeding at beginning of dialysis and increase risk of thrombosis at end of dialysis.

RECOMMENDATIONS

- Another protocol of Heparin as a continues or multiple boluses highly recommended providing effectiveness and safety.
- Conversion to single dose of low molecular weight heparin may be good alternative mimic the single bolus protocol.

REFERENCES

1. Hand book of dialysis, Jhon T.Daugirdas, 5th edition, 2015.
2. Oxford hand book of dialysis, Jeremy Levy, 4th edition, 2016.
3. Ouseph R, Brier ME, Ward RA. Improved dialyzer reuse after use of a population pharmacodynamics model to determine heparin doses. Am J Kidney Dis. 2000; 35(1):89–94.
4. Kossmann RJ, Gonzales A, Callan R et al.Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. Clin J Am Soc Nephrol. 2009;4(9):1459–1464
5. Murray PT, Reddy BV, Grossman EJ et al. A prospective comparison of three argatroban treatment regimens during hemodialysis in end-stage renal disease. Kidney Int. 2004;66(6):2446–2453
6. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. Nephron Clin Pract. 2008; 109(2):c80–c94.
7. Warkentin TE, Sheppard JA. Testing for heparin-induced thrombocytopenia antibodies. Transfuse Med Rev. 2006; 20(4):259–272.
8. Crowther MA, Cook DJ, Albert M, et al,Warkentin TE Canadian Critical Care Trials Group. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. J Crit Care. 2010;25:287–293
9. Wise PH, Hall AJ. Heparin-induced osteopenia in pregnancy. Br Med J. 1980;281(6233):110–111
10. Kwan BC, Kronenberg F, Beddhu S et al. Lipoprotein metabolism and lipid management in chronic kidney disease. J Am Soc Nephrol. 2007;18(4):1246–1261
11. Fellström BC, Jardine AG, Schmieder RE, et al.Aurora Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009; 360(14):1395–1407.
12. Wanner C, Krane V, März W et al.German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353(3):238–248Rodger MA, Kahn SR, Cranney A et al. Long-term dalteparin in pregnancy not associated with a decrease in bone mineral density: substudy of a randomized controlled trial. J Thromb Haemost. 2007;5(8):1600–1606
13. Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. Am J Med. 1995;98(6):575–586.
14. A. Davenport.What are the anticoagulation options for intermittent hemodialysis?Nat Rev Nephrol, 7 (2011), pp. 499-508 .
15. J.I. Shen, W.C. Winkelmayer.Use and safetyof unfractionated heparin for anticoagulation during maintenance hemodialysis. Am J Kidney Dis, 60 (2012), pp. 473-486
16. Kovalik E C. Hemodialysis anticoagulation. available at;https://www.uptodate.com/contents/hemodialysisanticoagulation
17. Wasse H, Gillen DL, Ball AM, et al. Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients, Kidney Int , 2003, vol. 64 (pg. 1455-1461
18. Grundstrom G, Christensson A, Alquist M et al. Replacement of acetate with citrate in dialysis fluid: A randomized clinical trial of short term safety and fluid biocompatibility. BMC Nephrol. 2013; 14:216
19. Fischer KG. Hemodialysis in heparin-induced thrombocytopenia. In:Warkentin TE, Greinacher A. eds. Heparin Induced Thrombocytopenia. 3rd ed. New York: MarcelDekker; 2003:509–530.
20. European best practice guidelines for hemodialysis (part 1). Nephrol Dial Transplant. 2002; 17(Suppl 7):63–71.
21. Roy A, Kalra V. Anticoagulation in Hemodialysis. JIMSA April-June 2012 Vol. 25 No. 2;107-109.