Original Article

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Effect of Heparin on Coagulation Tests: A Comparison of Continuous and Bolus Infusion in Haemodialysis Patients

Internal Medicine Section

ALI AKBAR NASIRI[1], SUDABEH AHMADIDARREHSIMA[2], ABBAS BALOUCHI[3], HOSEIN SHAHDADI[4], MAHDIYE POODINE MOGHADAM[5]

ABSTRACT

Introduction: Haemodialysis is one of the most conventional treatments of chronic renal failure. The risk of clot formation is high during haemodialysis due to regular contact of blood with the surfaces of foreign objects such as catheters, dialyzers' membrane, and other materials used for dialysis. Therefore, to prevent clot formation during haemodialysis, the dialysis system requires anticoagulation; this is usually done by heparin.

Aim: The present study aimed to compare two heparinization methods and determine the proper impacts of these methods.

Materials and Methods: In this quasi-experimental study, 80 haemodialysis patients covered by the dialysis center of Amir-al-momenin Hospital of Zabol were studied in two 40-member groups of heparin therapy methods of bolus injection and continuous infusion. PT and PTT were measured in blood samples collected from all patients before starting haemodialysis. The first group received 3000 units of heparin once the haemodialysis machine started to work and 2000 units of heparin two hours later as bolus injection. In the second group, 1500 units of heparin was injected at the start of dialysis after then, 5000 units of heparin (one mL) were mixed with 11 mL of distilled water and infused using a heparin injection pump up to half an hour before the end of dialysis. At 30 minutes after starting dialysis and at the end of 4 hours of haemodialysis, PT and PTT were measured and compared between the two groups.

Results: According to the results, the mean partial thromboplastin time in the bolus and continuous heparin-receiving group was 41.75±6.29 and 37.90±4.77, respectively, which was statistically significant (p=0.036). But PT was 14.45±1.82 in the bolus heparin group and 13.95±1.39 in the continuous heparin group, which was not significant according to the results of independent t-test (p=0.336).

Conclusion: The results indicated a statistically significant difference between the bolus heparin injection and the continuous heparin infusion groups in terms of coagulation tests in haemodialysis patients (p=0.036). Therefore, given the effects of heparin on coagulation, it was more effective in the bolus heparin group than the continuous infusion group. It is recommended to use the bolus method for heparin therapy during haemodialysis.

Keywords: Continuous heparin infusion, Heparin bolus injection, PT, PTT

INTRODUCTION

Haemodialysis is the most common method of treatment of end stage renal disease (ESRD) [1]. This therapy consists of a process of bilateral diffusion through a semi-permeable membrane during which metabolic wastes move from blood circulation toward dialysis fluid in their concentration gradient and the needed materials in the dialysis liquid are added to the blood [2]. Clot formation is very common during haemodialysis due to regular contact of blood with the surfaces of foreign objects [3] such as catheters, dialyzers' membrane, and materials used for dialysis. Blood is more susceptible to stick to the walls of these devices in patients with renal failure due to defects in platelet function [4]. Proper opening of arteriovenous lines is prerequisite for a desirable haemodialysis [5]. Impaired coagulation system is one of the most common causes of mortality in haemodialysis patients [6]. Although the process of haemodialysis reduces the risk of bleeding through excretion of poisonous toxins, it activates, on the other hand, the pathways of blood coagulation due to regular contact of blood (thrice a week) with external artificial surfaces such as catheters and dialyzers' membrane [7]. The non-physiological environment reduces the adequacy of dialysis and increases blood loss, nurses' workload, supplies, and hence treatment costs [8]. A proper coagulation system requires a balance in the amount of received heparin in order to prevent bleeding and clotting, especially since haemodialysis patients are very susceptible to long-term bleeding from fistula as well as gastrointestinal and intracranial bleeding [9]. In addition, haemodialysis patients are one of the few groups who receive heparin three times a week, exposing them to osteoporosis, aldosterone suppression, hyperkalemia, loss of lipids, and dysfunction of vascular endothelium [10]. In general, different methods exist for avoiding clot formation, with two methods being more common. In the first, 3000 units and 2000 units of heparin are injected as bolus into the beginning of arterial circuit once dialysis is started and after two hours, respectively. In the second, 1500 units of heparin are injected into the beginning of arterial circuit once dialysis is started and then 5000 units of heparin (one mL) are mixed with 11 mL of distilled water and infused using a heparin injection pump up to half an hour before the end of dialysis. However, no one has been recognized to be superior Vis the other [11]. Impaired PTT, on the other hand, leads to blood clotting in the coil of machine and reduces the adequacy of haemodialysis. Thus in order to lower bleeding rate, PTT should be reached to 1/8 of normal level immediately in haemodialysis and to 1/4 at the end [12]. To reduce clot formation, Askari et al., recommended injecting 2500 units heparin when dialysis is started and 2500 units 2 hours later [13]. According to the protocols in other countries, an initial dose of 50 U/kg is prescribed followed by continuous infusion of 500-1500 U/h [14]. Kazemi did not observed a significant difference in the rate of clot formation between the standard methods [15]. Clot formation in the filter reduces the exchange area and leads to removal of some of the blood from wastes exchange cycle, resulting in reduced dialysis efficiency and increased mortality [10]. Since there is no standard method for the type of heparin injection, and given the

complications and costs of different methods, it seems essential to choose the best injection method [2]. Due to the adverse effects of wrong injection of heparin on clot formation during dialysis and bleeding after pulling needle, and since anticoagulation measures requires awareness, skills, and experience of care providers in using different methods of heparinization in haemodialysis wards, and regarding the conflicting results of heparin administration.

AIM

The present study aimed to compare the two methods of heparinization and proper impact of each of these methods in haemodialysis patients in the dialysis center of Zabol City.

MATERIALS AND METHODS

In this quasi-experimental study, 80 haemodialysis patients referred to the dialysis center of Amir-al-momenin Hospital of Zabol, southeast of Iran, in 2013, with inclusion criteria were selected through the convenience sampling method and divided into two groups of 40 patients. Inclusion criteria were normal results of prothrombin time (PT) and partial thromboplastin time (PTT), lacking hepatitis C, history of blood transfusion during haemodialysis, history of bleeding, and receiving oral anticoagulants. Heparin was injected in the two groups as follows; the bolus injection group: 3000 units of heparin at the start of dialysis before reaching to the arterial chamber and 2000 units of heparin two hours after the start of dialysis as a bolus through the arterial line (the routine method which is performed in dialysis centers); the continuous injection group: injection of 1500 units of heparin at the start of dialysis before reaching to the arterial chamber and infusion of 5000 units of heparin (one mL) using a heparin injection pump up to one and a half hours before the end of the dialysis. Eleven milliliter of distilled water was used to dilute heparin in the second group. To measure PT and PTT, 2 mL of blood was collected from the arterial line before starting dialysis, half an hour after dialysis, and at the end of dialysis. PT and PTT were measured using Pars kits and the GT3000 device (USA). Finally, after completion of dialysis, the results of PT and PTT in the two groups were compared and the results were recorded. To avoid bias in the results of the dialysis machine, the dialysis set and solution, duration, flow rate, and total heparin and their expiration dates were the same in both groups.

Ethical consideration: The study was registered in the ethics committee of Zabol Medical Sciences University with No. 51/89. Written informed consent was obtained from patients and they could withdraw from the study whenever they wanted.

STATISTICAL ANALYSIS

Data were analysed with SPSS-18 (version 18, SPSS Inc., Chicago, IL) through descriptive statistics (relative frequency distribution, mean, and standard deviation) and inferential statistics (independent t-test and ANOVA). A p-value of less than 0.05 and confidence intervals (CI) of 95% were considered significant.

RESULTS

In this study, a total of 80 patients undergoing haemodialysis were divided into two 40-member groups of A and B. In group A (who received 3000 units of heparin once dialysis started and 2000 units of heparin two hours later as a bolus), 45% of the patients were female and 55% were male, and the minimum and maximum age was 39 and 63 years, respectively, with a mean age of 50.80±6.28 years. In group A, 25% of the participants were housekeeper, 20% were farmer, 25% were employee, and 30% were self-employed. In group B (who received 1500 units of heparin at the start of dialysis and 5,000 units (one mL) along with 11 mL of distilled water through a heparin infusion pump up to half an hour before the end of dialysis), 40% were female and 60% were male, and the minimum and maximum age was 35 and 70 years, respectively, with a mean age of 50.10±11.52 years. In group B, 15% of the participants were housekeeper, 25% were farmer, 25% were employee, and 35% were self-employed. Therefore, according to studies, it was estimated that the highest percentage of the subjects in group A were male; same as in group B, where 60% of haemodialysis patients were male, and most subjects in both groups were self-employed (30% in group A and 35% in group B). In terms of education, most of the haemodialysis patients participating in the study had a middle school degree and education levels of illiterate, third middle school, and diploma were more frequent among jobs of the haemodialysis patients in both groups of A and B [Table/Fig-1].

The mean partial thromboplastin time was 41.75±6.29 in group A and 37.90±4.77 in group B, which was significant according to independent t-test (p=0.036). However, PT was 14.45±1.82 in group A and 13.59±1.39 in group B, which was not significant according to independent t-test (p=0.336) [Table/Fig-2]. Comparison of the mean PTT and PT according to gender in both groups showed that the mean duration of PTT and PT in group A that received bolus heparin was more in men than women, and in group B with continuous infusion of heparin, PTT and PT were more in women than men, however, this finding was not statistically significant according to independent t-test [Table/Fig-3].

Comparison of the mean PTT and PT in terms of jobs in the two groups showed that the mean PTT was higher in housekeepers in both groups according to the results of ANOVA, although it was not significant based on one-way ANOVA. In group A, PT

Variables / Groups		Group A Mean±SD	Group B Mean±SD	p-value
Age		50.8±6.28	50.1±11.52	p=0.9
		N (%)	N (%)	
Gender	Male	22(55%)	24(60%)	p=0.2
	Female	18(45%)	16(40%)	
Job	Housewife	10(25%)	6(15%)	p=0.2
	Farmer	8(20%)	10(25%)	
	Employee	10(25%)	10(25%)	
	Self-employment	12(30%)	14(35%)	
Education	illiterate	8(20%)	4(10%)	p=0.7
	Primary school	4(10%)	6(15%)	
	Third Middle school	18(45%)	20(50%)	
	Diploma	8(20%)	2(5%)	
	Academic education	2(5%)	8(20%)	

[Table/Fig-1]: Demographic specifications.

	Group A	Group B	Independent t-test		
	Mean±SD	Mean±SD	p	T	F
PTT	41.75 ± 6.29	37.90±4.77	0.036	2.1	3.3
PT	14.45±1.82	13.59±1.39	0.336	0.9	0.9

[Table/Fig-2]: Comparison of the mean and standard deviation of PT and PTT in haemodialysis patients in groups A and B.

	Gender		Group A Mean±SD	Group B Mean±SD
PTT	Female		39.11±5.66	38.25±5.49
	Male		43.90±6.17	37.66±4.47
	Independent t-test	p	0.09	0.79
		T	1.73	0.26
PT	Female		14.22±1.09	14.37±1.06
	Male		14.63±2.29	13.66±1.55
	Independent t-test	p	0.62	0.27
		T	0.49	1.12

[Table/Fig-3]: Comparison of PTT and PT according to gender in two groups.

	Job		Group A Mean±SD	Group B Mean±SD
PTT	Housewife		44.8±7.56	41.66±7.63
	Farmer		40.25±2.62	37.40±4.21
	Employee		38.40±7.73	36.20±3.56
	Self-employment		43±5.33	37.85±4.77
	ANOVAs test	p	0.40	0.49
		F	1.02	0.82
PT	Housewife		13.25±0.50	14±1.73
	Farmer		16.40±2.40	14.20±1.64
	Employee		14.40±1.14	14.40±1.94
	Self-employment		13.66±1.03	13.42±0.53
	ANOVAs test	p	0.01	0.68
		F	4.40	0.51

[Table/Fig-4]: Comparison of PTT and PT according to job in two groups.

	Education		Group A Mean±SD	Group B Mean±SD
PTT	illiterate		43.25±4.99	39.60±3.64
	Primary school		36.50±2.12	37.50±4.79
	Third Middle school		43.85±6.89	38.60±36.87
	Diploma		42±7.48	36.16±4.16
	Academic education		36±1.41	0
	ANOVAs test	p	0.425	0.703
		F	0.476	1.02
PT	illiterate		15±2.82	13.80±1.09
	Primary school		13.50±0.57	13±0
	Third Middle school		14.42±1.81	14.60±1.81
	Diploma		14.60±1.81	13.80±1.09
	Academic education		14.50±0.70	0
	ANOVAs test	p	0.832	0.693
		F	0.362	0.491

[Table/Fig-5]: Comparison of PTT and PT according to education in two groups.

was higher in farmers compared to any other job (p=0.01), which was significant, and according to Tukey test performed following ANOVA, this significance was related to housekeepers and farmers (p=0.026) and the mean difference of 3.15. In group B, PT was higher in employees, but it was not significant [Table/Fig-4]. Comparison of mean levels of PT and PTT based on education in the two groups showed that the highest mean PTT was observed in participants with third middle school degree in group A and in illiterates in group B, which was not significant according to ANOVA test. The highest mean level of PT was seen in illiterates in group A and in participants with third middle school degree in group B. In addition, comparison of age between groups A and B with PT and PTT by Pearson correlation coefficient showed no significant relationship [Table/Fig-5].

DISCUSSION

The results showed that the mean partial thromboplastin time and mean prothrombin time were lower in the continuous heparin receiving group than the bolus heparin receiving group; and this lower rate reflects the lower impact of heparin and clot formation compared with the first method, i.e. the bolus injection method of heparin is more efficient according to the results of coagulation tests; this finding is not consistent with the results of Adib and Fatoorachi, because they believe that continuous infusion of heparin is a better method of preventing clot formation in terms of pharmacokinetic and hence recommended it. They also showed that bolus injection within 1-1.5 hours after administration of heparin results in a desired therapeutic level of PTT by 1.8 times, although, the level is reduced after that, while PTT remains constant in the continuous injection method. Therefore, Adib and Fatoorachi recommended using ordinary heparin in all cases through continuous infusion instead of interrupted injection [16].

Ward RA believed that changes in PTT before and after haemodialysis is a criterion of the coagulation status, and defined the difference of post-dialysis PTT with that of baseline as standard (less than or equal to ¼ of the initial PTT) and over-standard (more than ¼ of the initial PTT) [17]. Based on this definition, Dehghani et al., examined three methods; in the first method, the dialysis set was washed twice with 200 mL of normal saline after priming with 5000 units heparin; in the second method, 2000 units was injected as bolus and 1000 U/h was infused until the beginning of the fourth hour; in the third method, 2500 units was injected at first and 2500 units two hours later. The incidence of thrombosis was higher in the first method than the second and third methods, and it was significantly higher in the third method than the second. In the standard range, PTT was significantly higher in the first method compared with the second. The second method, in which 2000 units was injected as bolus and 1000 U/h was infused until the beginning of the fourth hour was associated with a lower risk of clot formation. According to Dehghani, the second method was safer, because clot formation was lower in the second method than the other two methods, and since PTT increment in the second method was in the standard range in 52% of the cases [18], this finding of Dehghani's study is consistent with the present study regarding higher efficiency of the bolus method. Sabry A et al., compared the first (bolus injection) and second (continuous injection) methods for 6 months in Saudi Arabia, and reported that clot formation in the second method was lower than the first; this corresponds with the present study [19]. According to Sagedal et al., both methods were appropriate. They believe that anticoagulation during haemodialysis can be achieved by administering an initial dose and maintaining it with continuous infusion or another bolus during dialysis [12]. In a study by Kazemi et al., the incidence of clot formation in the first method (bolus) in all dialysis centers in Kerman Province was significantly more than the other two methods (p≤0.05). The partial thromboplastin time of whole blood in the study of Kazemi was 30 seconds after an hour and reduced to 15 seconds after two hours. Therefore, it can be expected that over time and due to not administrating heparin, the risk of clot formation in the dialyzer increases, especially after the second hour [15]. Kazemi's study showed that the conventional method (5000 units PBH) is implemented more than two other methods in haemodialysis centers, which is consistent with the present study [15]. Hofbauer et al., believed that anticoagulation with a single administration of heparin during haemodialysis is not enough (due to its short half-life) and suggested to use low molecular weight heparin with a longer half-life in case of its administration [20].

Apsner et al., showed that ordinary heparin is usually infused continuously in intermittent haemodialysis to prevent clotting in the dialysis system; in this case, low molecular weight heparin is preferred to ordinary heparin [16]. JY Vos et al., warned about the risks of bolus hourly prescription of heparin including haemorrhage and anaphylactic reactions and tried to point out the positive results of continuous infusion and suggested it as routine haemodialysis in the dialysis wards [21]; this is not consistent with the present study. In a study, entitled adequacy and effectiveness of anticoagulant bolus with enoxaparin for chronic haemodialysis patients, Klingle R et al., concluded that anticoagulation with enoxaparin with a bolus dose over 4 hours is suitable for patients with chronic renal failure and recommended a dose of 70 U/kg [22].

LIMITATIONS

This study has limitations that should be noted; the results were obtained from PTT and PT tests which are the most common methods to assess the effects of heparin therapy, but they may

be altered by biological factors. Therefore, it is recommended to study more closely the effect of heparin therapy in terms of other factors and clinical indicators and with higher sample sizes at different times [23].

CONCLUSION

As a result, there was a significant difference between heparin bolus injection and heparin continuous infusion in terms of coagulation tests in haemodialysis patients, and the effect of heparin was higher in the bolus method than the continuous infusion. Therefore, this method helps prevent clotting in haemodialysis system and can avoid indiscriminate administration of heparin which predisposes individuals to bleeding; thus it is recommended to use the bolus heparin method in heparin therapy during haemodialysis.

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PARTICULARS OF CONTRIBUTORS:
1. Faculty of Medicine School, Department of Anaesthesiology and Pain Medicine, School of Medicine, Zabol University of Medical Science, IR Iran.
2. MSc Student of Nursing, Department of Medical Surgical, Student Research Committee (SRC), School of Nursing and Midwifery, Zabol University of Medical Sciences (zbmu), Zabol, IR Iran.
3. MSc Student of Nursing, Department of Medical Surgical, Student Research Committee (SRC), School of Nursing and Midwifery, Zabol University of Medical Sciences (zbmu), Zabol, IR Iran.
4. MSc in Nursing, Department of Medical Surgical, School of Nursing and Midwifery, Zabol University of Medical Sciences, Zabol, IR Iran.
5. MSc in Nursing, Department of Medical Surgical, School of Nursing and Midwifery, Zabol University of Medical Sciences, Zabol, IR Iran.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Hosien Shahdadi,
Ferdowsi St, Nursing and Midwifery Faculty, Zabol University of Medical Sciences, Zabol, Postal Code: 9861456789, IR Iran.
E-mail: hosienshahdadi@gmail.com

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