

The Effects of Heparinization Methods of Hemodialysis Sets on Coagulation Status

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ABSTRACT

One of the most effective measures in increasing the dialysis adequacy is to use an appropriate administration method of anticoagulants to prevent clot formation in the hemodialysis system. Therefore, the present research was carried out to find the most proper anticoagulation method in hemodialysis patients. 176 hemodialysis patients admitted to the dialysis centers of Kermanshah University of Medical Sciences under the two methods of anticoagulation with heparin (continuous infusion and intermittent bolus group) via convenient sampling method participated in this quasi-experimental research. The dialyzer observation and Partial Thromboplastin Time (PTT) test were utilized for evaluating the coagulation and clotting formation of the arterial and venous chambers. The research was carried out in the before and after comparative form. Data collection tools are the checklist of doing hemodialysis and demographic and background features. Finally, SPSS16 statistical software was used to analyze the data. The blood clots occurrence in the dialyzer was considerably more frequent in the intermittent method than infusion method in the second, third and fourth dialysis hours (the end of dialysis) ($P < 0.05$). However, no significant difference was seen in PTT comparison of the two methods. Based on the findings, for better anticoagulants, infusion method can be suggested to dialysis centers. In addition, because the changes in the PTT is more stable using this method, bleeding risk does not threaten the patient.

Keywords: Heparin, Methods of hemodialysis, Hemodialysis sets, Coagulation status

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INTRODUCTION

In the 21st century the most prominent event that is faced by communities and healthcare personnel is the prevalence of increasing chronic diseases. One of these diseases that has significant side effects for the patient is the Chronic Kidney Disease (CKD) [1]. Hemodialysis is one of the major treatments for patients suffering from chronic kidney disease [2, 3]. In

this way, patients are usually under dialysis 2 to 3 times a week and each time will be approximately 4 hours. An extracorporeal circuit is a prerequisite for the delivery of adequate dialysis. When performing hemodialysis due to the flow of blood outside the body (extracorporeal) and its exposure to hemodialysis machine's different surfaces (e.g. dialyzer membranes, catheters, lines, and chambers), the coagulation cascade, leukocytes,

and platelets are activated and this increases the clot formation possibility [4-11]. Also, due to platelet dysfunction in patients with renal kidney failure, the risk of Sticking blood to the walls of these devices is greater [3].

During hemodialysis, an anticoagulation of the extracorporeal circuit of the dialysis system to prevent clot formation is required [2, 3, 10-17]. The oldest and most commonly used anticoagulant in dialysis procedures is heparin [13, 18-24]. Use of unfractionated heparin as an anticoagulant and a principle in hemodialysis, was one of the key advances leading to the rapid development of hemodialysis [25]. Heparin reduces the activity and accumulation of platelets by binding to the antithrombin III factor and subsequently disabling coagulation factors II, IV, VI, VII [2, 5, 18]. To prevent bleeding or clotting in the patient, the dose of heparin received should be balanced [3]. A little of heparin causes clots in the dialyzer that may result in significant blood loss, waste treatment reduced performance and reducing the adequacy of dialysis due to mechanical obstruction of the dialyzer membranes [3, 26]. In contrast, a lot of heparin led to bleeding especially from fistula as well as gastrointestinal and intracranial bleeding, which occurs 5-26% of treatments [2, 3]. Because of the short half-life of heparin and to ensure proper anticoagulation during a hemodialysis sessions, the use of heparin requires an initial dose and consequently a maintenance dose [8, 12]. For hemodialysis, heparin can be injected into arterial line based on the different regimes. But in the most common method, heparin as the base bolus dose followed by continuous infusion or through repeated bolus can be administered for patients without increasing risk of bleeding [4, 11, 19, 21, 27, 28].

Appropriate adequacy of dialysis is achieved by removing at least 70% of the urea present in the body. This will be achieved only when the maximum capacity of dialyzer is used and there should not be clotting in capillary tubes in dialyzer [5, 29]. Clot formation in the dialysis circuit, especially dialyzer, reduces the efficiency of the dialyzer and ultimately reduces the adequacy of dialysis (one of the important causes of dialysis patients' mortality); Because the dialyzer membrane's capability in the removal and transfer of waste products of blood is one of the factors affecting the dialysis adequacy [26, 30, 31]. Some studies have shown that heparin

continuous infusion has better results than intermittent boluses [21-36]. Nasiri *et al.* study showed that based on the results of coagulation tests, the injection of heparin by bolus method to prevent clot formation in the hemodialysis circuit is more effective [3]. In contrast, a number of studies have considered both of them as appropriate methods [19, 27, 37]. Kazemi has shown in a study that there is not a significant difference between the two methods of intermittent and infusion in the clot formation rate [2].

Subjects

Considering the above-mentioned issues and the increasing number of patients with chronic kidney disease and hemodialysis patients followed by complications caused by dialysis, all necessary efforts must be used to increase hemodialysis adequacy in these patients. Prevention of clot formation by an appropriate administration of anticoagulant (heparin) is one of the most important measures in this field. So, for determining the most proper method of anticoagulation in these patients, during the study, the researchers tried to consider and compare the two methods of heparinized hemodialysis set and its effect on clot formation in hemodialysis patients referring to dialysis centers in Kermanshah University of Medical Sciences in 2012; based on achieved results, appropriate strategies should be adopted in this regard and the most appropriate method of anticoagulation should be provided to the relevant organizations.

MATERIALS AND METHODS

The method of this research is based on the study by Sabry *et al.* [12] Because both of these studies have been extracted from a thesis with the same procedure. However, in the study of Sabry *et al.*, the effects of heparinization on dialysis adequacy has been studied.

176 hemodialysis patients referring to dialysis centers of Kermanshah University of Medical Sciences, who had inclusion criteria participated in this quasi-experimental study, under the two methods of anticoagulation with heparin through convenient sampling method.

Tools for data collection include background and demographic features and the checklist of doing hemodialysis. Questions about age, gender,

weight, height, education, occupation, marital status, residence, dialysis history, monthly income, and number of hemodialysis sessions per week formed the demographic part. The checklist part contained patient's dialysis information (including hemodialysis machine type, dialyzer type, the dialyzer number, dialysate flow rate, blood flow rate per minute, dialysate sodium, dialysate temperature, patient's blood pressure, vascular access process, patient's weight gain, ultrafiltration (weight loss) rate in every session, weight before and after dialysis, duration of hemodialysis in a sessions, the amount of heparin intake, a companion during hemodialysis, and information related to two methods of heparin administration (including the PTT before and after dialysis, the rate of clot formation in arterial- venous chambers and dialyzer). It was a quasi-experimental study (before and after comparison); i.e. during two times of referring, the patient was under one of the methods of anti-coagulation every time and at the end of four hours of hemodialysis, the amount of clotting in venous and arterial chambers and dialyzer in both methods were recorded and compared. To eliminate the effect of previous method on the other method, the two methods were done with one-week interval. These two methods were:

Infusion method

In this method, the total amount of heparin received by the patient was diluted with 19 ml of normal saline solution. In the dialysis commencement and before blood's reaching to the arterial chamber, the patients received their usual half dose of heparin (10 ml) as a bolus via the arterial line. After 3-5 minutes of starting dialysis and restoring blood flow in hemodialysis circuit, the remaining half-dose infusion of heparin (10 ml) by the infusion pumps was prepared and set to the end of the third hour and infusion was discontinued one hour before the end of dialysis and the patient did not take any heparin.

Intermittent method

In this method, at the commencement of dialysis and before the blood's reaching to the arterial chamber, the patients received their usual half dose of heparin as a bolus via the arterial line. After that, the remaining half of the dose was injected through divided bolus doses every 1.5

hours until the end of the third hour and the patient did not receive any heparin at the last hour.

In both methods, the amount of heparin received, type of heparin and heparin expiration date were the same. Also in both cases the same dialysis parameters were used to perform dialysis procedures (Prime, blood flow rate, solution flow rate, temperature, weight loss, wash the dialyzer, etc.).

In order to evaluate coagulation status PTT tests, viewing arterial and venous chamber and the dialyzer were used. That in the beginning (before heparin injection) and at the end of hemodialysis, the sample of PTT was taken from the patient and delivered to a laboratory and the samples were evaluated by a fixed laboratory expert with the same kit and device. In addition, the arterial and venous chamber and the dialyzer, every time after washing with normal saline, during and after hemodialysis were analyzed for clot formation. The clot intensity was divided into four grades including no clot (if dialyzer is smooth and clean = 0 points), mild clot (less than one quarter of the dialyzer diameter = 1 point), average clot (between one quarter to half of the dialyzer diameter = 2 points), severe clot (more than a half of the dialyzer diameter = 3 points).

The SPSS software version 16, and descriptive statistics (mean, standard deviation and two-dimensional tables as the number and percentage) and analytical statistics (ANOVA and Wilcoxon tests) were utilized to analyze the data.

RESULTS AND DISCUSSION

55.1% of the total 176 participants of the research was male. The mean age and weight of the patients were 55.84 ± 13.44 yrs and 64.9 ± 13.5 kg, respectively. In terms of salary, 69.9 percent of people did not have any income. The majority of patients were illiterate (49.4%), unemployed (67.1%), and married (81.2%). Moreover, 88.6 % of patients lived in the city and 58.2% of them were alone during their dialysis sessions. Hemodialysis treatment duration, on mean, was 30.7 ± 24.9 months. 10.8% of patients were under dialysis twice a week and 89.2% of them three times per week. Hemodialysis machines used in 93.2% of cases were Fresenius and dialyzer used in the 89.8% of cases was the PS dialyzer. In the 64.2% of cases of fistula, patients were used as vascular access and 39.8% of participants were

undergoing hemodialysis sessions in the morning shift. The mean blood flow rate (pump speed) was 279.35 ± 35.66 ml per minute (minimum 200 and maximum 360 ml) (**Table 1**).

Table 1. The mean (\pm SD) of hemodialysis patients' dialysis characteristics undergoing hemodialysis.

Variable (Dialysis characteristics)	Results
The blood flow rate (ml per min)	279.35 ± 35.66
Dialysis solution temperature ($^{\circ}$ C)	36.96 ± 0.23

Table 2. Comparison of the incidence of clot dialyzer in two different methods of hemodialysis set anticoagulation with heparin at different hours.

Timing intensity of clotting	infusion		intermittent		P value
	Number	Percentage	Number	Percentage	
First hour	None	151	85.8	147	0.33
	Mild	25	14.2	27	
	Medium	---	---	2	
Second hour	None	140	79.5	125	0.008
	Mild	36	20.5	47	
	Medium	---	---	4	
Third hour	None	129	73.3	111	0.01
	Mild	44	25	59	
	Medium	3	1.7	6	
Fourth hour	None	108	61.3	84	<0/001
	Mild	58	33	72	
	Medium	10	5.7	20	

Table 3. Comparison of mean (\pm SD) of PTT in hemodialysis patients in two different methods of hemodialysis set anticoagulation with heparin

PTT(seconds)	Before dialysis	After dialysis	Difference(Changes)	P- value a
Infusion	31 ± 48.56	22.94 ± 44.2	39.15 ± 4.89	0.717
intermittent	34 ± 47.94	23 ± 42.8	39.66 ± 4.87	0.251
P value	0.008	0.4	0.459	

^a Comparison of PTT before and after dialysis

The average clot rate in the fourth hour in infusion and intermittent methods were 5.7% and 11.4%, respectively. Based on Wilcoxon test results, no significant difference was observed between the two methods regarding the formation of clot in the dialyzer in the first hour ($P = 0.33$). This compares in the second ($P = 0.008$), third ($P = 0.01$) and fourth hours ($P < 0.001$) of dialysis indicated a significant difference between the two methods.

The chamber arterial clot formation rate in the fourth hour, in the infusion and intermittent methods were 21% and 25%, respectively. Also, no clot was observed in both methods in the first and second hours of dialysis in venous chamber. But comparing the incidence of clotting in arterial and venous chambers at different hours of dialysis using the Wilcoxon test indicated no significant difference between the two methods ($P > 0.05$).

Sodium hemodialysis solution (mEq per liter)	138 ± 0.5
Dialysis time (h)	3.45 ± 0.32
Systolic blood pressure (mm Hg)	130.5 ± 20.5
Ultrafiltration (L in a dialysis session)	2.0175 ± 1.002

The evaluation of coagulation was done based on PTT changes and clot observation in venous - arterial chambers and dialyzer in infusion and intermittent method (**Tables 2 and 3**).

According to Wilcoxon test results comparing the coagulation based on changes in PTT (differences before and after), indicated no statistically significant differences between the two methods ($P = 0.459$).

The results showed that the clotting occurrence in the dialyzer in the intermittent method was significantly greater than the infusion method. A number of studies have been conducted in this regard in their results were expressed that heparin continuous infusion had more positive results than intermittent bolus [4, 21, 23, 34, 36]. A study entitled "Heparinisation in chronic Hemodialysis treatment: bolus injection or continuous homogeneous infusion?" conducted by DeVos *et al.* [33] stated that administered heparin by continuous infusion is more useful in patients who are bleeding after dialysis or suffer from anaphylactic reactions. Ouseph *et al.* also stated that the basic dose followed by a

continuous infusion in terms of anticoagulant effect, provides more uniform and stable surface than one or two bolus dose [32]. Brunet *et al.* [35] investigated the pharmacodynamics of heparin during and after dialysis sessions and showed that continuous infusion of heparin provides sufficient and safety anticoagulant effects for the patient and this anticoagulant effect reduces immediately after the end of the dialysis session. As well as Dehghani *et al.* [36] examined three methods of heparin anticoagulation and showed that the second method (continuous infusion of heparin) was safer, because clot formation was lower in this method than the other two methods. These results are consistent with our study. In contrast Nasiri *et al.* [3] study showed based on the results of coagulation tests, the injection of heparin by bolus method to prevent clot formation in the hemodialysis circuit is more effective.

However, a number of studies have suggested in their results that using both infusion and intermittent methods is suitable for anticoagulation during hemodialysis and there is no difference between the two methods [11, 19, 27, 28, 37]. Kazemi *et al.* [2] in their study in terms of the rate of clot formation between the two intermittent and infusion methods did not find a statistically significant difference. Also Oshvandi *et al.* and Stefoni *et al.* did not obtain statistically significant differences in their study in terms of clot formation in the arterial and venous chambers and dialyzer through different anti-coagulation techniques [6, 9]. The studies above were not consistent with the results of our study. May be it is related to insufficient sample size in the Kazemi *et al.* [2] study and comparing heparin with other anticoagulants (not comparing the two methods of heparin administration) in other studies.

A significant difference existed between the two methods regarding clot formation in the dialyzer which could be due to this cause: Except the last hour in the continuous infusion, heparin exists continuously in dialysis circuit in remaining hours; whereas in the intermittent method heparin is injected in this path in the form of bolus and in divided doses.

Another important finding of this study is related to the assessment of coagulation status. Which states that the comparison of PTT changes (PTT difference before and after) in the two methods indicated no significant difference, whereas the

changes of PTT in the infusion method were greater than intermittent method. Also PPT changes at the end of dialysis were more stable in infusion method. Similarly, Stefoni *et al.* in their study with regular monitoring of APTT indicated that: 30 minutes after using heparin in the infusion method, a peak appeared on the APTT charts, but at the end of dialysis APTT rates were in the therapeutic range and quite stable [9]. Dehghani *et al.* [36] also showed that PTT increment in continuous infusion heparin in 52% of the cases, it was within the standard range. Baradaran *et al.* investigated the effect of the two types of anticoagulants (heparin and LMWH) on the rate of PTT dysfunction in their study. They showed that by using heparin (in the intermittent method) at the end of dialysis, the PTT dysfunction rate in most cases was equal or less than one-fourth of the baseline measure [38]. The findings of the present study coincide with the results of the studies above that may be related to the use of PTT test to assess coagulation status, which is similar to our study. In contrast the results of Nasiri *et al.* [3] survey showed that the mean partial thromboplastin time in the method of heparin injection in the form of bolus, was higher than Continuous infusion method, i.e. based on the results of coagulation tests, the injection of heparin by bolus method to prevent clot formation in the hemodialysis circuit is more effective. PTT stability at the end of dialysis with infusion method could be due to continuous injecting of heparin in this path.

In this study the changes rate of PTT did not show significant statistical differences in the two methods, which could be due to intrapersonal differences in the metabolism of heparin. In this regard, it is suggested that a similar study should be done with emphasis on heparin dosing based on body weight.

Among the limitations of the current study was the impossibility of ACT in dialysis centers in Kermanshah. In this regard, it is suggested that a similar study should be done based on ACT, TAT and platelet aggregation to assess coagulation status.

CONCLUSION

In this study, we found that in terms of coagulation status, the incidence of clotting in the dialyzer in infusion method is less than intermittent method and also the mean change of

PTT in infusion method was more than intermittent one. So we can say that the infusion method compared with intermittent method is more appropriate for anticoagulation during hemodialysis and since the changes of PTT is more stable in it, bleeding risk does not threaten the patients. So we can say that anticoagulation by the right method is one of the effective factors in reducing clot formation in hemodialysis patients.

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