Original Article

Anticoagulation treatments related different types of vascular access on maintenance hemodialysis patient: A multicenter epidemiological investigation

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ABSTRACT

Objective: The objective was to increase the understanding of vascular access in hemodialysis and evaluate hemodialysis-related anticoagulation treatments and the associated hemorrhagic or thrombotic complications. **Materials and Methods:** In this study, an epidemiological investigation was conducted in 1175 patients who underwent hemodialysis in seven blood purification centers in northern Chinese. The patients were divided into two groups based on the vascular access they used: Arteriovenous fistula (AVF) group and central venous catheter (CVC) group. The similarities and differences of anticoagulation and hemorrhagic, thrombotic complications were compared between two groups. **Results:** Arteriovenous fistula was the most frequently used vascular access, and heparin was the most commonly used anticoagulant. Patients in CVC group experienced significantly greater rates of low molecular weight heparin (LMWH) administration and had a higher rate in achieving thrombotic complications than those in AVF group. There were no significant differences in LMWH dosages in patients with thrombotic complications, as well as the proportion of patients who received anti-platelet drugs. Heparinized catheter lock solutions were excessively high in this study, which may lead to a risk of hemorrhage. **Conclusion:** Hemodialysis-related anticoagulation treatments in China require additional improvements, especially for the patients using CVC as vascular access. There is an urgent need to develop clinical evaluation studies of anticoagulation treatments for achieving more standardized and targeted treatments.

Key words: Anticoagulants, hemodialysis, vascular access

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INTRODUCTION

It is very important to establish and maintain a well-functioning vascular access for hemodialysis patients. Permanent vascular access has three methods, including arteriovenous fistula (AVF), grafted vessels fistula, and long-term indwelling central venous catheter (CVC). Vascular access complications induced by different causes are important reasons that result in hospitalization rate increase of hemodialysis patients; wherein the thrombosis is the most common complication. MacRae *et al.*[1] reported that the incidence of catheter-related thrombosis was 41% in hemodialysis patients. Therefore, a reasonable anticoagulant therapy is very important to the maintenance of vascular access function. In this study, we investigated the use and maintenance of vascular access in 1175 patients who underwent hemodialysis in seven blood purification centers in northern Chinese,

focused on assessing the status of anticoagulant therapy and hemorrhagic, thrombotic complications in patients with different vascular access.

MATERIALS AND METHODS

Research object

Hemodialysis patients data were collected in seven hospitals blood purification center of four cities: Beijing, Shenyang, Harbin, Dalian. Seven blood purification centers are named, Chinese PLA General Hospital (including two blood purification centers), the First Affiliated Hospital of Dalian Medical University, General Hospital of the General Staff of Chinese PLA, the First Affiliated Hospital of Harbin Medical University, the First Affiliated Hospital of China Medical University and the First Affiliated Hospital of Chinese PLA General Hospital. The survey was conducted from December 2012 to February 2013. Case selection criteria: Hemodialysis patients were in seven blood purification centers and signed informed consent. Case exclusion criteria:

1. Dialysis age <1-month;
2. Age <14 years;
3. Clinical data were incomplete.

The study was reviewed by the People's Liberation Army General Hospital Medical Sciences Ethics Committee; all subjects signed informed consent.

Survey items and contents

1. Patients general situation: Name, gender, age, weight, and blood pressure, hemoglobin, platelet count, serum lipids before dialysis and urea clearance index (Kt/v), etc.;
2. The kind and dose of anticoagulant, CVC lock case;
3. Oral anticoagulation situation;
4. Primary disease: Primary glomerulonephritis, diabetic nephropathy, hypertensive renal damage and other diseases;
5. Hemorrhagic complications: Subconjunctival hemorrhage, gastrointestinal hemorrhage, mucocutaneous hemorrhage, puncture hordeolum hemorrhage, cerebral hemorrhage, etc., (hemorrhage events occurred from before survey to after hemodialysis);
6. Thrombotic complications: Venous thrombosis, arterial thrombosis, vascular access blocked, cerebral infarction, myocardial infarction, pulmonary embolism, etc., (thrombotic events occurred from before survey to after hemodialysis).

Statistical analysis

The data were analyzed by software SPSS 18.0. Normal distribution measurement data were represented with the mean ± standard deviation; abnormal distribution was expressed as median and interquartile. Normal distribution of data, measurement data were compared using *t*-test or analysis of variance between multiple mean pair-wise comparisons using Student-Newman-Keuls q-test; Count data were compared using the Chi-square test; Abnormally distributed data were compared using the F-test or U-test. $P < 0.05$ was considered as a statistically significant difference.

RESULTS

General conditions

A total of 1175 patients with complete information obtained from 7 hemodialysis centers, including 555 female and 620 male; mean age was 56 years; mean duration of dialysis was 49 ± 2 months. Of which 1066 cases (90.7%) were AVF patients and 109 cases (9.3%) were CVC patients, no patient selected graft fistula within 7 centers. Male and primary glomerulonephritis patients were more likely to choose AVF as vascular access ($P < 0.01$) while female and primary diabetic patients were more likely to choose CVC ($P < 0.01$). The dialysis duration of patients chosen AVF was significantly longer than the patients chosen CVC (51.76 months vs. 24.59 months, $P < 0.01$). Predialysis blood pressure, hemoglobin concentration, platelet levels, lipids and Kt/v difference of AVF and CVC group of patients were not statistically significant [Table 1].

Anticoagulant treatment situation

In 1175 cases of patients, 646 cases (55.0%) applied unfractionated heparin (UFH) as an anticoagulant, 492 cases (41.9%) patients with low molecular weight heparin (LMWH) as an anticoagulant, the remaining 37 patients were treated with other anticoagulants. Applications proportion of UFH was significantly higher than the LMWH ($P < 0.01$). In AVF group, patients more chose UFH (56.3%) as an anticoagulant; and in CVC group, LMWH (52.3%) utilization rate was higher than UFH (42.2%); compared with AVF group, LMWH utilization rate in patients selected CVC was significantly higher (52.3% vs. 40.8%, $P < 0.01$). Overall average dose of UFH was (76.64 ± 20.65) u/kg, that of LMWH was (52.81 ± 16.77) u/kg; anticoagulant dose, the difference was not statistically significant ($P > 0.05$). In the CVC group, patients were treated with 5000 u/mL of heparin for catheter lock after hemodialysis. In 1175 cases, 242 cases (20.6%) were treated with oral anti-platelet drugs, including aspirin, clopidogrel, ticlopidine, and dipyridamole. Ratio of oral anti-platelet drug in AVF group and CVC group was 20.7% and 19.3%; the difference was not statistically significant ($P > 0.05$) [Table 2].

Thrombotic, hemorrhagic complications and anticoagulation treatment

Among 1175 cases of patients surveyed, there were 224 cases (19.1%) in the hemodialysis before the survey

appeared to thrombotic complications, including 126 cases of vascular access thrombosis (56.3%), 39 cases of myocardial infarction (17.4%), 38 cases of cerebral infarction (17.0%), 20 cases of limb arterial and venous thrombosis (8.9%) and one case of pulmonary embolism (0.4%). There were 353 cases (30.0%) patients had hemorrhagic complications, including mucocutaneous hemorrhage (including skin ecchymosis; gastrointestinal hemorrhage; the nasal mucosa, gums, subconjunctival hemorrhage; increased menstrual flow, etc.), 297 cases (84.1%), a puncture needle bleeding (referring after hemodialysis pull out the needle puncture, needle oppression still bleeding after 30 min), 38 cases (10.8%), 12 cases of cerebral hemorrhage (3.4%) and retinal hemorrhage in 6 cases (1.7%). In CVC group, 34 cases (31.2%) complicated by thrombosis, significantly higher than the AVF patients (190 cases, 17.8%) ($P < 0.01$); and of 34 cases with thrombotic complications, 28 cases (accounting for 25.7%) for vascular access thrombosis, and in 190 cases of AVF group, only 98 cases (accounting for 9.2%) for vascular access thrombosis, Incidence of vascular access-related thrombotic complications in CVC group was significantly higher than that of AVF group ($P < 0.01$). Hemorrhagic complications in two group were 325 cases (30.5%) and 28 cases (25.7%); the difference was not statistically significant. In 353 cases of hemorrhagic patients, 40.2% (142 cases) selected LMWH as an anticoagulant, was significantly higher than the patients with thrombotic complications 31.7% (71 patients) ($P < 0.01$); Similarly, whether AVF group or CVC group, LMWH used in patients with hemorrhagic complications were higher than in patients with thrombotic complications (AVF group: 38.2% vs. 28.4%, $P < 0.01$; CVC group: 64.3% vs. 50.0%, $P < 0.01$). In patients with thrombotic Complications, the utilization rate of LMWH in CVC group was significantly higher than that of AVF group (50.0% vs. 31.7%, 50.0% vs. 28.4%, $P < 0.01$). Both in the general population, or in the AVF group or CVC group, the usage dose of UFH in patients with thrombotic complications was significantly higher than that in patients with hemorrhagic complications ($P < 0.05$); in the overall group and AVF group, the usage dose of LMWH in patients with thrombotic complications was significantly higher than that in patients with hemorrhagic complications ($P < 0.05$); but in the CVC group, there was no statistical significance of LMWH between these two kinds of patients ($P > 0.05$). LMWH dose in patients with hemorrhagic complications, CVC group, was significantly higher than the overall group and AVF group ($P < 0.01$). In the overall patient group and the AVF group, proportion of oral anti-platelet drugs in patients with thrombotic complications was significantly higher than that in patients with hemorrhagic complications (overall: 36.6% vs. 23.8%, $P < 0.01$; AVF group: 37.4% vs. 23.4%, $P < 0.01$); but in the CVC group, proportion of oral anti-platelet drugs in

Table 1: General information of 1175 patients

No. of patients	Age (a)	Sex female, n (%)	Dialysis age (months)	SBP (mmHg)	DBP (mmHg)	Hemoglobin (g/L)	Blood platelet ($\times 10^9$/L)	Serum cholesterol (mmol/L)
Total (1175 cases)	56.00±15.46	553 (47.1)	49.24±4.41	142.43±25.60	82.52±15.84	104.08±25.64	184.52±61.54	4.00±1.04
AVF group (1075 cases)	55.83±15.39	485 (45.5)	51.76±44.78	142.84±25.92	82.78±16.03	104.84±25.92	185.37±61.36	3.97±1.02
CVC group (109 cases)	57.57±16.17	68 (62.4)	4.59±31.50	138.45±22.00	80.03±13.73	96.44±21.74	175.92±63.05	4.24±0.78
P	0.30	0.001	0.000	0.62	0.71	0.15	0.77	0.09
	Serum TG (mmol/L)	Kt/v	Dialysis frequency (time/week)	Time of every dialysis (h)	The number of primary disease *n* (%)			
					Glomerulonephritis	Diabetic nephropathy	Hypertensive renal damage	Other
Total	1.75±0.98	1.38±0.61	2.82±0.38	4.00±0.05	631 (53.7)	227 (19.3)	112 (9.5)	205 (17.5)
AVF group (1075 cases)	1.75±0.89	1.39±0.55	2.82±0.37	4.00±0.04	586 (55.0)	195 (18.3)	99 (9.3)	186 (17.4)
CVC group (109 cases)	1.79±1.50	1.35±0.72	2.80±0.50	3.98±0.09	45 (41.2)	32 (29.4)	13 (11.8)	19 (17.6)
P	0.07	0.07	0.67	0.87	0.008	0.007	0.39	1.00

SBP: Systolic blood pressure; DBP: Diastolic blood pressure, TG: Triglyceride, AVF: Arteriovenous fistula, CVC: Central venous catheter

patients with hemorrhagic or thrombotic complications had no significant difference ($P = 0.79$) [Table 3].

DISCUSSION

Arteriovenous fistula as a permanent vascular access, with a relatively simple surgical operation, inexpensive, easily obtained, less long-term patency rate and complications, is a priority vascular access currently recommended by K/DOQI guidelines.[2] The results of the study showed that AVF utilization rate in all patients was 90.7%, CVC utilization rate was 9.3%; consistent with previous research, AVF still is the preferred vascular access; but large venous catheter usage has close to 10%, compared with the previously reported 5.6%.[3] Studies have shown a higher AVF utilization rate in young, male and nondiabetic patients,[4] consistent with the results of this study; and our results showed that duration of dialysis in patients with AVF was significantly longer than that in CVC patients, about two times than the latter; this aspect may be associated with higher survival rates in patients with CVC compared with AVF patients,[4] on the other hand it may be related to most dialysis patients has not been established AVF in China. Although a number of studies have confirmed that using AVF vascular access is better than CVC in hemodialysis, but for patients with severe heart failure, severe and refractory hypotension, vascular conditions cannot complete AVF and must be carried out in hemodialysis with immature AVF, CVC is the best choice.[2,5] However, the use of CVC can cause thrombus, infection, vascular stenosis, dysfunction, fibrin sheath formation and other complications,[6] not only affect the dialysis adequacy, but also increase the economic burden. Survey results of hemodialysis patients in north America, the cost of catheter maintenance, and related complications treatment is of up to $1 billion.[7,8] The results of the study showed that the incidence of thrombotic complications in CVC group was significantly higher than that in the general population, almost twice than that of the AVF group. Most of vascular access itself formed thrombosis, which may relate to piping material, not standardized tube closure operation after dialysis, many use of intravenous catheter in diabetes and other factors. Several studies have confirmed that AVF survival time is 1.6-3.6 times than CVC patients.[9,10] Therefore, For hemodialysis patients using CVC, it is particularly important to maintain their blood stable, have adequate and effective anticoagulant therapy; the reason of death in hemodialysis patients is approximately 1/2 of cardiovascular disease (CVD),[11] and therefore the proper application of anti-rational coagulation therapy is an important aspect of reducing CVD and mortality in hemodialysis patients.[12] However at present, the authoritative guidelines did not specially emphasize on its anticoagulant therapy,[13] including the choice of anticoagulant, dosage adjustments, monitoring indicators and primary prevention of thrombosis and other complications. The results of this study showed that UFH was still as the main anticoagulant in the overall sample and AVF patients, while CVC patients are more choices LMWH. Although compared with heparin, LMWH can reduce the effect of hemodialysis on blood, including thrombosis, fibrin deposition, cell damage, etc.;[14] however, this effect

Table 2: Anticoagulant treatment of vascular access in each group

Anticoagulant therapy	UFH		LMWH		Oral antiplatelet drugs *n* (%)
	n (%)	Dose (u/kg)	*n* (%)	Dose (u/kg)	
Total	646 (55.0)	76.64 ± 20.65	492 (41.9)[a]	52.81 ± 16.77	242 (20.6)
AVF group	600 (56.3)	76.60 ± 20.74	435 (40.8)[a]	52.54 ± 16.56	221 (20.7)
CVC group	46 (42.2)	77.08 ± 19.58	57 (52.3)[a,b]	54.96 ± 18.35	21 (19.3)

[a]$P < 0.01$ versus UFH group, [b]$P < 0.01$ versus AVF group. AVF: Arteriovenous fistula, CVC: Central venous catheter, UFH: Unfractionated heparin, LMWH: Low molecular weight heparin

Table 3: Anticoagulant treatment in patients with hemorrhage and thrombus in each group

Groups	UFH		LMWH		Antiplatelet drugs *n* (%)
	n (%)	Dose (u/kg)	*n* (%)	Dose (u/kg)	
Total					
Hemorrhage	194 (55.0)	68.12 ± 22.49	142 (40.2)[a]	50.38 ± 17.30	84 (23.8)
Thrombus	148 (66.1)	73.82 ± 20.86[b]	71 (31.7)	57.77 ± 19.49	82 (36.6)
AVF group					
Hemorrhage	185 (56.9)	68.15 ± 22.71	124 (38.2)[a]	49.58 ± 17.05	76 (23.4)
Thrombus	131 (68.9)	73.82 ± 20.79[b]	54 (28.4)	59.07 ± 17.86	71 (37.4)
CVC group					
Hemorrhage	4 (14.3)	67.44 ± 7.24	18 (64.3)[a]	57.37 ± 18.68	8 (28.6)
Thrombus	17 (50.0)	73.80 ± 2.09[b]	17 (50.0)	54.89 ± 24.47	11 (32.4)

[a]$P < 0.01$ versus the thrombosis group, [b]$P < 0.01$ versus bleeding group. AVF: Arteriovenous fistula, CVC: Central venous catheter, UFH: Unfractionated heparin, LMWH: Low molecular weight heparin

has been reported with little effect in hemodialysis patients using CVC and not enough to prevent the occurrence of thrombotic complications.[15]

In this study, although more patients in CVC group selected LMWH, but a higher thrombotic complications than the overall average also confirmed this.

The results of the study showed that for patients with thrombotic complications, anticoagulants (including UFH and LMWH) doses of the overall group and AVF group were higher than hemorrhage patients; in CVC group, only for patients with thrombotic complications increased dosage of UFH, did not been adjusted for LMWL dose, its use even lower doses in patients with hemorrhage. It directed although the kind of anticoagulant of patients with venous catheter types was considered by clinical, but the dose was no adjusted according to the clinical complications. The results of data analysis of 2815 hemodialysis patient showed that aspirin can reduce the risk of thrombotic complications in hemodialysis patients without increasing the risk of hemorrhage.[16] A survey of New York City Blood Purification Center showed the situation of underutilized aspirin in hemodialysis patients.[17] The results of this study appeared in the general population, the utilization of anti-platelet drugs, including aspirin, about 20%, far below the proportion of 42.4~45.1% in patients with aspirin, displayed in the Dialysis Outcomes and Practice Patterns Study hemodialysis system.[18] In the overall group and the AVF group, for patients with thrombosis, the utilization of anti-platelet was significantly higher; but in the CVC group, although it is higher in patients with thrombotic complications compared with other two groups, but its utilization of anti-platelet was lower than the first two groups, and in patients with hemorrhagic complications, use rate of anti-platelet drug actually increased, suggesting that for hemodialysis patients used CVC as for vascular access, use of anti-platelet drugs is lack of standardized, and lack of appropriate adjustments.

The results of abroad showed lock solution of catheters central venous existed obvious leaks.[19] After the 5000 u/mL of heparin lock 10 min, activated partial thromboplastin time (APTT) could increase 373.7% while the 1000 u/mL of heparin lock APTT increased only 22.2%; and clinical anticoagulant effects between the two groups did not significantly differences, it is recommended CVC heparin lock concentration 1000 u/mL.[20] The results in the present study, CVC heparin lock concentration was of 5000 u/mL. This was bound to bring patients the risk of hemorrhage. On the other hand, in theory in order to play the role of anticoagulation, heparin only depends on the presence of blood antithrombin III, while CVC's volume is limited, the number of antithrombin III is also limited, and therefore there is no need to give too high concentration heparin. Currently, it is very necessary to carry out appropriate research on CVC dose anticoagulants, promote the rational use of anticoagulants

CONCLUSION

Autogenous AVF is still the most commonly used as the vascular access in hemodialysis patients in China. It exists higher thrombotic events when CVC as a vascular access, so we more choose LMWH as anticoagulants, but did not increase the dose of LMWH, nor increase oral anti-platelet drug usage; CVC concentration of heparin lock is too high, it may bring patients the risk of hemorrhage. It is need to carry out clinical evaluation, establish the appropriate anticoagulation program, and promote standardization of anticoagulation in hemodialysis patients.

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