The Incidence and Risk Factors of Proximal Vein and Central Vein Stenosis in Acute Arteriovenous Graft and Fistula Thrombosis in Dialysis Patients

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Background: *The incidence and risk factors of the proximal vein and central vein stenosis in Thai hemodialysis patients has not been well documented.*
Objective: *1) To evaluate incidence and risk factors of the proximal vein and central vein stenosis in acute arteriovenous graft and fistula thrombosis in dialysis patients. 2) To investigate the time to rethrombosis of vascular access after revision and risk factors for rethrombosis.*
Material and Method: *Sixty two patients who need the revision of thrombosed hemodialysis access in Vascular and Transplantation Unit, Ramathibodi Hospital, were included in our study. All patients underwent graft or fistula thrombectomy with patch angioplasty or jump graft and venogram in order to detect proximal vein and central vein stenosis. In this group, the treatment is balloon angioplasty. Patient's demographics data, timing of access creation and dialysis initiation, previous central venous catheter placement and its patency after the revision were analyzed.*
Results: *From 62 patients, one was excluded due to contrast allergy. Eighteen patients (30%) had central or proximal vein stenosis; 11 (61%) were proximal vein stenosis and 7 (39%) were central vein stenosis. Central vein stenosis was found in 11.5% (7/61) of this group of patients and 18% (11/61) for proximal vein stenosis. They were treated with balloon angioplasty with the technical success rate of 83% (15/18). Rethrombosis was recorded in 37.7% (23/61) at a median time of 2.3 months (range 1.5 weeks to 11 months) after revision of the access thrombosis. Independent risk factors for rethrombosis were the presence of central vein and proximal vein stenosis (hazard ratio 3.74), DM (hazard ratio 3.07), and the duration of previous vascular access (hazard ratio 1.02).*
Conclusion: *The incidence of central and proximal vein stenosis in acute arteriovenous graft and fistula thrombosis was 30% and had impact to the rethrombosis after access revision.*

Keywords: *Central vein stenosis, Central vein occlusion, Renal failure, Hemodialysis, Arteriovenous graft, AV fistula*

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Central vein stenosis and occlusion is an important problem in dialysis patients. The usual presentations of these patients are swollen arms, superficial vein dilatation and the access malfunction. The global incidence of central vein stenosis and occlusion is about 30%[1]. However, the number was not well studied in Thai hemodialysis patients.

The incidence of central vein stenosis and occlusion is strongly associated with a history of central venous catheter insertion; 40% in subclavian vein and 10% in internal jugular vein. The pathogenesis of central vein stenosis and occlusion is the inflammatory response and intimal hyperplasia caused by the central venous catheter insertion, the increased blood flow, and the repetitive turbulence of the AV access[2].

Direct physical damage from the movement of the catheter tip or body against a vessel wall can potentially result in thrombin generation, platelet activation, and inflammatory response. Endothelial injury with subsequent changes in the vessel wall results in the development of microthrombi, smooth muscle proliferation, and central vein stenosis[3]. Central venography is the gold standard for the diagnosis of central vein stenosis and occlusion since they are highly

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associated with the quality of hemodialysis and the vascular access patency.

In Thailand, most of the hemodialysis patients have initiated dialysis with central venous catheter. Therefore, they are at high risk of central vein stenosis or occlusion. According to NKF-KDOQI guidelines, venography was recommended before permanent access creation for patients with a prior subclavian line in ipsilateral extremity. Once the central venous stenosis and occlusion, the ipsilateral access placement should be avoided.

We postulate that some hemodialysis patients who come for treatment of acute arteriovenous graft or fistula, thrombosis may also have occult stenosis of the proximal and/or central vein (with no clinical sign or symptom before the access thrombosis). If the stenosis is not detected and treated it would lead to early failure of the access after revision.

So our study is aimed to investigate the incidence and the predisposing factors of central vein and proximal vein stenosis in acute arteriovenous graft and fistula thrombosis in dialysis patients in Ramathibodi Hospital. The secondary end point of this study is to study the risk factors for rethrombosis after revision of arteriovenous graft and fistula.

Material and Method

The present study was performed as a prospective cohort study. It was approved by ethical committee of Ramathibodi Hospital. All patients with acute AV graft or AVF thrombosis who needed a revision of hemodialysis access in Vascular and Transplantation Unit, Ramathibodi Hospital between April to December 2013, were included in the study. Patients with an allergy of iodine contrast and known cases of, or had clinical signs of central vein stenosis were excluded. Balloon angioplasty was performed in the patient who underwent graft thrombectomy with patch angioplasty or jump graft and venogram revealed proximal vein or central vein stenosis. The central and proximal vein stenosis is defined as venous outflow stenosis (VOS) which criterion for diagnosis is at least 50% narrowing of the central veins of the thorax that included the superior vena cava, brachiocephalic vein, subclavian vein, subclavian-cephalic vein junction and proximal veins including the cephalic vein and basilic vein[4].

Data collection included patient demographics (age, gender, underlying disease, body mass index (BMI)), timing and type of access, history of central venous catheter insertion, duration of dialysis and access patency after revision.

Statistical analysis was performed on the collected data. A p-value <0.05 was considered to be significant. The incidence of the proximal vein and central vein stenosis were presented as mean, standard deviation and percentage. T-test and Chi-square test and univariable Cox proportional hazards regression analysis were used for the risk factors for VOS and rethrombosis. All analyses were performed using SPSS version 11.0.

Results

A total of 62 patients were included in the study (one patient was excluded due to contrast allergy). There were 61 thrombosed vascular access assigned to the revision during the study period. Venogram of the proximal and central vein was obtained prior to the intervention. In case of central or proximal vein stenosis, balloon angioplasty was attempted. The vascular access was repaired using standard methods. Patients were evaluated for the recurrent thrombosis (rethrombosis) after the procedures.

Baseline data and characteristics, and risk of VOS

There were 61 patients with vascular access thrombosis. VOS was found in 18 patients (30%) with 7/18 (39%) were at central vein (brachiocephalic vein) and 11/18 (61%) were at proximal vein (cephalic vein).

The incidence of central vein stenosis was 11.5% (7/61) and none of them had clinical signs (occult stenosis). The incidence of Proximal vein stenosis was 18% (11/61).

The amount of contrast media used in the procedure was significantly different between the two groups but this is probably of no major clinical importance (*e.g.* need more contrast media to visualize and treatment by balloon angioplasty). There was no clear risk factor for the development of VOS. However, there were several factors that show a tendency toward the development of VOS such as male gender, longer duration of previous vascular access, the higher number of previous operation, and shorter duration of current vascular access. All patients with VOS underwent balloon angioplasty and had a success rate of 83% (15/18).

Vascular access rethrombosis and risk factors for rethrombosis

After surgical revision of vascular access thrombosis and correction of venous outflow stenosis, patients were followed for a median time of 2.3 months (range, 1.5 weeks to 11 months). The rethrombosis rate

Table 1. Baseline characteristics of study population

Characteristic	No VOS (n = 43)	With VOS (n = 18)	*p*-value
Age, mean (±SD)	60.8 (±15.1)	59.8 (±12.5)	0.798
Left side: No. (%)	27 (63)	12 (67)	0.774
Upper arm access: forearm access (%)	10: 33 (23: 77)	6: 12 (33: 67)	0.414
Gender (male): No. (%)	16 (37)	11 (61)	0.087
BMI (kg/m^2), mean (±SD)	24.8 (±5.0)	22.7 (±3.7)	0.118
Hypertension: No. (%)	36 (84)	13 (72)	0.303
DM: No. (%)	26 (61)	10 (56)	0.722
Dyslipidemia: No. (%)	20 (47)	11 (61)	0.298
Duration of HD (months): (range)	24 (2 to 84)	24 (1 to 122)	0.471
Duration of current access: (range)	14 (1 to 60)	10 (1 to 60)	0.101
Previous catheter access: No. (%)	35 (81)	15 (83)	0.857
Duration of catheter access: (range)	4 (0 to 60)	4 (0 to 48)	0.880
Previous vascular access: No. (%)	11 (26)	8 (44)	0.147
Duration of previous vascular access: (range)	0 (0 to 68)	0 (0 to 113)	0.092
Radiopaque media used (mL), mean (±SD)	15.1 (±6.9)	26.1 (±11.2)	<0.001

Table 2. Comparison of characteristics between patients with and without rethrombosis

Characteristic	No rethrombosis (n = 38)	With rethrombosis (n = 18)	*p*-value
Age, mean (±SD)	61.8 (±15.0)	58.3 (±12.9)	0.352
Left side: No. (%)	24 (63)	15 (65)	0.871
Upper arm access: forearm access (%)	7: 31 (18: 82)	9: 14 (39: 61)	0.075
Gender (male): No. (%)	18 (47)	9 (39)	0.530
BMI (kg/m^2), mean (±SD)	24.2 (±4.5)	24.1 (±5.0)	0.934
Hypertension: No. (%)	31 (82)	18 (78)	0.752
DM: No. (%)	20 (53)	16 (70)	0.192
Dyslipidemia: No. (%)	20 (53)	11 (48)	0.716
Duration of HD (months): (rang)	24 (1 to 72)	27 (4 to 122)	0.180
Duration of current access: (range)	16.5 (1 to 60)	11 (1 to 60)	0.022
Previous catheter access: No. (%)	30 (79)	20 (87)	0.430
Duration of catheter access: (range)	3.5 (0 to 14)	6 (0 to 48)	0.267
Previous vascular access: No. (%)	9 (24)	10 (43)	0.106
Duration of previous vascular access: (range)	0 (0 to 40)	0 (0 to 113)	0.052
Radiopaque media used (mL), mean (±SD)	16.7 (±8.9)	21.1 (±10.5)	0.089
VOS: No. (%)	7 (18)	11 (48)	0.015
Successful PTA (n = 18): No. (%)	7/7 (100)	8/11 (73)	0.245

was 37.7% (23/61) within this follow-up time.

The presence of venous outflow stenosis is an important risk factor of vascular access early rethrombosis after revision (*p*-value = 0.015).

From a multivariable statistical analysis, independent risk factors for early (within 1 year) rethrombosis after revision of vascular access included the presence of VOS, DM, and the longer duration of previous vascular access (Hazard ratio 3.74, 3.07 and 1.02 respectively).

Discussion

The incidence of central vein and proximal vein stenosis in this study was about 30%. The presence of ipsilateral VOS was a strong predictor of early rethrombosis of vascular access. The compromised hemodynamics could contribute to the vascular thrombosis even after the successful balloon angioplasty. DM is a well-known and plausible predisposing cause of vascular atherosclerosis and thrombosis.

Table 3. Potential risk factors for rethrombosis, univariable cox proportional hazards regression analysis

Risk factors	Hazard ratio (95% CI)	*p*-value
Age, per year increase	0.987 (0.960 to 1.01)	0.331
Right side vs. left side	0.951 (0.399 to 2.26)	0.910
Upper arm vs. forearm access	1.99 (0.858 to 4.62)	0.109
Men vs. women	1.19 (0.514 to 2.76)	0.684
BMI, per unit (kg/m^2) increase	0.999 (0.912 to 1.10)	0.999
Hypertension vs. no hypertension	0.727 (0.268 to 1.98)	0.532
DM vs. no DM	1.84 (0.754 to 4.47)	0.180
Dyslipidemia vs. none	1.01 (0.442 to 2.30)	0.986
Duration HD, per month increase	1.02 (1.00 to 1.03)	0.026
Duration current access, per month increase	0.950 (0.905 to 0.996)	0.039
Previous catheter access vs. none	1.38 (0.408 to 4.64)	0.607
Duration catheter access, per month increase	1.04 (1.00 to 1.07)	0.046
Previous vascular access vs. none	2.21 (0.942 to 5.20)	0.068
Duration previous vascular access, per month increase	1.02 (1.01 to 1.04)	0.002
Radiopaque media used, per mL increase	1.04 (0.995 to 1.08)	0.081
Central vein stenosis vs. none	3.57 (1.56 to 8.19)	0.003
Successful PTA vs. not (n = 18)	0.266 (0.067 to 1.05)	0.060

Table 4. Independent risk factors for rethrombosis from multivariable cox regression analysis

Risk factor	Hazard ratio (95% CI)	*p*-value
Presence of central vein stenosis	3.74 (1.47 to 9.53)	0.006
Presence of DM	3.07 (1.16 to 8.14)	0.024
Duration of previous vascular access (per month increase)	1.02 (1.00 to 1.04)	0.027

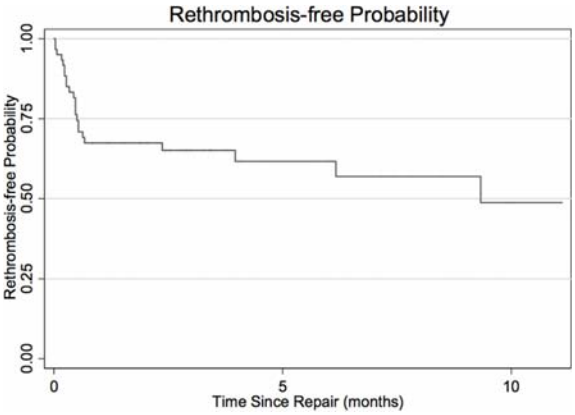

Fig. 1 Overall rethrombosis-free probability.

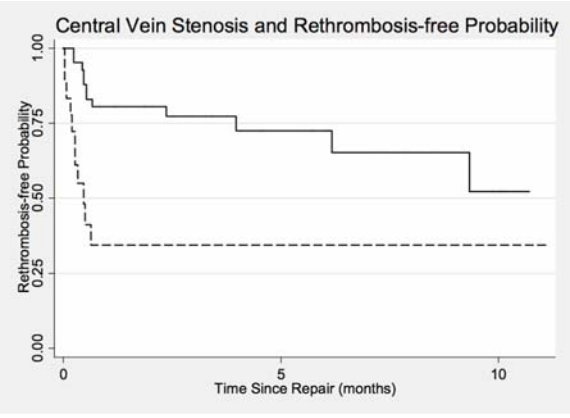

Fig. 2 Rethrombosis-free probability: solid line, no VOS; dashed line, with VOS.

The significance of the previous vascular access duration was not clear. Only former operation on the ipsilateral extremity could contribute to the later vascular access rethrombosis. It had no influence over the contralateral extremity. This was assumed that a previous access had compromised the venous outflow allowing a higher risk of thrombosis if another access

were to be performed on the same arm. This risk was duration dependent; such that the longer the duration of previous access, the higher the risk of rethrombosis. Although this study cannot clearly identify the risk factor for the development of proximal vein stenosis it can demonstrate the risk factors for early re-thrombosis after revision of the access thrombosis which was presence of proximal vein stenosis, diabetes and the longer duration of ipsilateral previous vascular access. Base on findings from this study, we recommended venography to be performed in all patients during the revision of vascular access thrombosis if there is no contraindication because adequate correction of venous outflow stenosis is crucial to obtain successful treatment.

Since the venous outflow stenosis signifies the higher risk of re-thrombosis after the access revision, the contralateral limb should be evaluated and preserved as a preferred site for a new vascular access placement in the future.

What is already known on this topic?

The incidence of central vein stenosis or occlusion in hemodialysis patients reported in the literature is about 30%. The usual presentations of these patients are swollen arms, superficial vein dilatation and the access malfunction. The development of central vein stenosis is strongly associated with a history of central venous catheter insertion.

Although most of Thai hemodialysis patients have initiated dialysis with central venous catheter there is no report of the incidence of central vein stenosis in these patients.

In some patients who come for treatment of acute arteriovenous graft or fistula, thrombosis may also have occult stenosis of the proximal and/or central vein (without clinical sign or symptom). If the stenosis is not detected and treated it would lead to early failure of the access after revision. So our study is aimed to evaluate the incidence and risk factors for the development of proximal and central vein stenosis in acute arteriovenous access thrombosis patients.

What this study adds?

The incidence of venous outflow stenosis in acute arteriovenous graft and fistula thrombosis was 30%. Location of stenosis was at the central vein (11.5%) and at the proximal vein (18%) and none of them had the clinical sign or symptoms prior to the access thrombosis.

Although this study cannot clearly identify the risk factor for the development of proximal vein stenosis it can demonstrate the risk factors for early re-thrombosis after revision of the access thrombosis which was presence of proximal vein stenosis, diabetes and the longer duration of ipsilateral previous vascular access.

Base on findings from this study, we recommended venography to be performed in all patients during the revision of vascular access thrombosis if there is no contraindication because adequate correction of venous outflow stenosis is crucial to obtain successful treatment.

Since the venous outflow stenosis signifies the higher risk of re-thrombosis after the access revision, the contralateral limb should be evaluated and preserved as a preferred site for a new vascular access placement in the future.

Potential conflicts of interest

None.

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ปัจจัยเสี่ยงและอุบัติการณ์เกิดภาวะหลอดเลือดดำส่วนต้นและส่วนกลางตีบตันในผู้ป่วยที่มีการอุดตันเฉียบพลันของเส้นเลือดฟอกเลือด

ขวัญชัย ลาวัลย์วงษ์, วิวัฒน์ ถิระพานิช, โสภณ จิรสิริธรรม, ปิยนุช พูตระกูล, สุทัศน์ ฮ้อศิริมานนท์, ภาณุวัฒน์ เลิศสิทธิชัย

ภูมิหลัง: *ในปัจจุบันยังไม่มีการศึกษาหรือรายงานถึงอุบัติการณ์เกิดการตีบตันของ proximal vein และ central vein ในผู้ป่วยที่ฟอกเลือดเพื่อบำบัดรักษาภาวะไตวายเรื้อรังในประเทศไทย*

วัตถุประสงค์: *1) เพื่อศึกษาอุบัติการณ์และปัจจัยเสี่ยงของการเกิดการตีบตันของ proximal vein และ central vein ในผู้ป่วยฟอกเลือดที่มารับการรักษาภาวะการอุดตันแบบเฉียบพลันของเส้นฟอกเลือด 2) ระยะเวลาและปัจจัยเสี่ยงในการเกิดการอุดตันซ้ำของเส้นฟอกเลือดในผู้ป่วยกลุ่มนี้*

วัสดุและวิธีการ: *การศึกษาทำในผู้ป่วยเส้นฟอกเลือดอุดตัน 62 ราย ที่มารับการรักษาที่สาขาวิชาศัลยศาสตร์หลอดเลือดและปลูกถ่ายอวัยวะ โรงพยาบาลรามาธิบดี หลังจากได้รับการผ่าตัดเอาลิ่มเลือดอุดตันในเส้นฟอกเลือดออก thrombectomy ร่วมกับการทำ patch angiography หรือ jump graft แล้วผู้ป่วยทุกรายได้รับการฉีดสี venogram เพื่อหาภาวะการตีบตันของ proximal vein และ central vein ซึ่งถ้าตรวจพบผู้ป่วยกลุ่มนี้จะได้รับการรักษาเพิ่มด้วยการทำ balloon angioplasty บันทึกข้อมูลพื้นฐานผู้ป่วย, ระยะเวลาที่เริ่มทำเส้นฟอกเลือดและเริ่มฟอกเลือด, ประวัติการใส่สายสวนหลอดเลือด central vein, และระยะเวลาที่ใช้งานได้ของเส้นฟอกเลือดหลังผ่าตัดแก้ไขเพื่อมาวิเคราะห์*

ผลการศึกษา: *ผู้ป่วยหนึ่งรายใน 62 รายถูกคัดออกเนื่องจากมีประวัติแพ้สารทึบรังสีในผู้ป่วย 61 ตรวจพบว่า 18 ราย (30%) มีการตีบของ central vein หรือ proximal vein ซึ่ง 11 ราย (61%) เป็นการตีบที่ proximal vein และ 7 ราย (39%) ตีบที่ central vein ในผู้ป่วยกลุ่มนี้ พบการตีบของ central vein ได้สูงถึง 11.5% (7/61) และตีบที่ proximal vein 18% (11/61) การรักษาด้วย balloon angioplasty สำเร็จ 83% (15/18) หลังการผ่าตัดแก้ไข พบว่าเกิดการอุดตันซ้ำของเส้นฟอกเลือด 37.7% (23/61) ที่ median time 2.3 เดือน (1.5 สัปดาห์ ถึง 11 เดือน) ปัจจัยเสี่ยงในการเกิดการอุดตันซ้ำของเส้นฟอกเลือดคือ มีการตีบของ central vein หรือ proximal vein (hazard ratio 3.07), และระยะเวลาที่เคยใช้เส้นฟอกเลือดมาก่อน (hazard ratio 1.02)*

สรุป: *ในผู้ป่วยที่เส้นฟอกเลือดอุดตันมีการตีบของ central vein หรือ proximal vein ร่วมด้วยสูงถึง 30% และเป็นปัจจัยเสี่ยงต่อการอุดตันซ้ำของเส้นฟอกเลือดหลังการผ่าตัดแก้ไข*