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DURATION AND FREQUENCY OF CATHETERIZATION IN CENTRAL VEIN STENOSIS: A CASE CONTROL STUDY

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ABSTRACT.

Introduction: Central vein catheterization (CVC) is a major risk factor for central vein stenosis (CVS). Repetitive contacts of the CVC to the blood vessel wall results in inflammation, microthrombi, hyperplasia of the intima, fibrosis and thus development of CVS. This article reports the correlation of duration and frequency of CVC in patients with CVS.

Methods: A matched case control study was conducted in Cipto Mangunkusumo Hospital. Samples were gathered from the medical record from 2013 to 2015.

Results: Fifty four out of 717 patients underwent CVC for HD had CVS. 32 patients with CVS included in the study with 128 non-CVS patients included as control. Duration of CVC >6 weeks does not increase the risk of CVS (p= 0.207), whilst the odds ratio of CVS on the frequency of CVC >2 times is 30 times compared to those underwent <2 times (p= <0.001).

Conclusion: The frequency of CVC >2 times increased the risk of CVS. Longer duration of CVC for HD did not increase CVS rate.

Introduction

Chronic kidney disease (CKD) is a global health problem, with the increasing prevalence and incidence of kidney failure. The increase in the prevalence of chronic kidney disease is due to the increasing number of elderly population, as well as the prevalence of diabetes and hypertension. Systematic review by Hill et al (2016) states the prevalence of global chronic kidney disease is 13.4%.1 RISKESDAS data (2013) noted the prevalence of chronic kidney disease in Indonesia was 0.2%.2 Indonesian renal registry noted that in 2015 there were 30,554 patients with terminal renal failure undergoing routine hemodialysis.3 Data from the US renal data system (2013) recorded 103,382 patients undergoing routine hemodialysis from 117,162 patients diagnosed with terminal renal failure. A total of 88.4% of these patients were being installed a hemodialysis catheter for vascular access in the first hemodialysis.[4]

Installation of a central venous catheter for hemodialysis access is a major factor in central venous stenosis, which manifests upper limb and facial edema, collateral venous dilation of the face, neck and chest, and ulceration and tissue damage.5 Novelty in this study was a longer catheter compared to KDOQI suggested, usage is often repeated (> 2 times), and there is no consensus on hemodialysis with a catheter. In other countries, cimino access has been prepared in CKD stage IV patients. According to Schumacher et al. (1989) the incidence of central venous stenosis in a population of patients undergoing routine hemodialysis is 14%, 23-29% in the US and Canada, while there is still no data in Indonesia.6 Some studies show predisposing factors for central venous stenosis after installation of a central venous catheter for hemodialysis access depend on the type of catheter (short term, long term, diameter), duration of catheter use, and location of catheter placement (subclavian vein, jugular vein). Macrae et al (2005) suggested the prevalence of central venous stenosis by 41% in 133 patients with hemodialysis catheter dysfunction. The mean number of catheter use is 1.6 times with a mean duration of 5.5 weeks in patients with central venous stenosis. Repeated contact with blood vessel walls can cause inflammation, muscle cell migration and thrombus formation which can alter the flexibility of blood vessels and increase blood vessel intralumen pressure. The end result of this process is the occurrence of central venous stenosis.7 Management of central venous stenosis is by endovascular and operative, which requires large costs. Installation of hemodialysis access in 2013 – 2015 at RSCM was recorded as many as 944 patients and in 675 patients were placed a central venous catheter. Data on the prevalence of central venous stenosis at RSCM in 2013 – 2015 reached 7.53%. Case of central venous stenosis in RSCM often occur at the prolonged duration of catheter use and the frequency of repeated insertion, therefore it needs to be investigated.

Theoretical Review

Central venous stenosis (CVS) is an abnormal narrowing of the lumen that occurs in the axillary, subclavian, brachiocephalic, or superior vena cava veins. Veins are considered to have stenosis if there is evidence of a narrowing of 30% of the diameter of the venous lumen, with or without collateral circulation. CVS is the most common complication after central venous catheter insertion.8 Data on the incidence and prevalence of CVS to date is very limited. CVS prevalence in the US and Canada is 23-29%. Installation of hemodialysis access in 2013-2015 at RSCM was recorded as many as 944 patients in which 675 patients were placed in a central venous catheter. Data on CVS incidence at RSCM in 2013 – 2015 was recorded at 7.53%. Risk factors for CVS are related to the frequency of insertion, duration of use, location and position of the catheter tip, history of catheter-related infections, and material and catheter size. CVS caused by bronchogenic carcinoma or lymphoma must be excluded because CVS is due to mass suppression, not due to vascular endothelial damage.5,9

The risk of CVS increases with the frequency of repeated catheter insertion and the duration of long-term use. Macrae (2005) suggested 41% prevalence of CVS in 133 patients with hemodialysis catheter dysfunction. The mean number of catheter use is 1.6 times with a mean duration of 5.5 weeks in patients with subclavian venous stenosis.7 Hernandez (1998) reported that 42 patients with subclavian catheter placement had persistent stenosis after six

months of use, occurred in repeated use (2 times compared to 1.58 times), long-term duration (49 days versus 29 days), frequent hemodialysis (21 times versus 12 times) and more susceptible to infection (66.6% versus 33.3%).[11]

Trerotola (2000) stated that the mean time of CVS in subclavian vein catheter placement was 36 days, while the internal jugular vein was 142 days.14 Macrae (2005) study of 133 hemodialysis patients performed venography, 55 patients (41%) of whom experiencing CVS. Patients with CVS had a longer duration of dialysis (43 versus 34 months) and a history of previous dialysis catheter (53/55 versus 59/78).[7]

The study of Cimochowski (1990) showed that patients with a central venous catheter placed on the subclavian vein had a 50% incidence of CVS, whereas CVS did not occur in the internal jugular vein.15 CVS prevalence was higher at the left than right catheter site; it was found that CVS occured at 50% (7/14) on the left installation side compared to 0.9% (1/117) on the right side.[15]

The relationship of catheter infection with the occurrence of CVS is still unknown, but it is suspected that the installation of a long-term central venous catheter triggers inflammation of the venous wall resulting in blood flow stasis which predisposes to the appearance of infection. Incidence of CVS is also higher in the usage of a bigger cathether diameter (12-14 French) rather than small diameter (4-8 French). Grove (2000) states a linear relationship between the diameter of a catheter and the number of CVS (1% in size 4 French, 6.6% in size 5 French, and 9.8% in size 6 French).8 CVS often occurs in placement of CVC with the catheter tip in the central superior vena cava and at the border of the superior vena cava with the right atrium. To reduce the risk of CVS, the placement of the catheter tip should lie in the inferior part of the right atrium even though this placement has the risk of intraatrial thrombus.8 Rigid catheter materials such as polyethylene, Teflon, polyurethane occur more frequently in CVS than silicon. This is due to a greater inflammatory reaction.[8]

The pathomechanism of CVS begins with a catheter that induces trauma to the venous endothelium. This is due to several factors such as the body responding to the catheter as a foreign object which triggers an inflammatory reaction, catheter friction against the venous wall when respiration and when moving, increased blood flow and turbulence of blood flow after the establishment of arteriovenous fistula. Turbulence can cause venous wall thickening or an increase in platelet deposits.[5]

Venous wall trauma initiates thrombin formation, platelet activation, and expression of selectin-P with an inflammatory response, and leukocyte activation which causes the release of myeloperoxidase and platelet aggregation which induces inflammatory reactions, thrombus formation and changes in venous wall histology. Inflammatory reaction via CD34 + also causes migration of smooth muscle cells from the tunica media or from circulation to the intima which causes smooth muscle proliferation and the occurrence of atherogenesis.8 Thrombus formation due to platelet aggregation, atherogenesis, collagen and smooth muscle proliferation causes thickening of the venous wall so that veins lose their vascular tone, thus triggering CVS. Anatomical factors also affect the occurrence of CVS, the vein on the left side has a narrower diameter, is longer and winding so that the contact of the catheter with the vein wall is higher which triggers an inflammatory reaction.[8]

CVS is generally asymptomatic and only 50% of patients have clinical symptoms. CVS should be suspected in patients with a history of central venous catheter insertion, especially with a history of repeated insertion and long-term catheter use. Clinical manifestations in accordance with the location of the occurrence of obstruction of blood flow.5 In subclavian venous stenosis there is edema, hyperemia, pain, cellulitis in the ipsilateral upper extremity with the location of the catheter that can extend to the breast, and pleural effusion can occur.5 In brachiocephalic stenosis there is edema of the upper extremity and ipsilateral face to the location of catheter placement. Bilateral stenosis of the brachiocephalic vein can cause CVS syndrome. CVS is characterized by the occurrence of bilateral edema of the upper extremities, face, neck, and the appearance of collateral venous dilation of the chest and neck. CVS can also cause connective tissue edema in the neck so it can suppress the airway.8 CVS can cause stasis of blood flow and increased venous pressure resulting in backflow that causes venous aneurysm, collateral venous dilation, elongated blood clots after hemodialysis, hemodialysis which is not adequate, until it causes stasis of blood flow and decreased blood flow velocity so that thrombosis arises at the site of access to hemodialysis.8

Asymptomatic CVS can be detected by angiography. CVS can be diagnosed from history and physical examination. On history taking a previous history of central venous catheter placement, both repeated and long-term catheter insertion, whereas physical examination revealed swelling of the upper extremities, face, collateral vein dilation on the face, neck, and chest after catheter insertion. The diagnosis can be confirmed by duplex ultrasound examination which can show blood flow in the vein, detecting loss of respiration to the diameter. Venography is the gold standard for the diagnosis of CVS.5

In patients with chronic obstruction and collateral formation, close observation is sufficient. Intervention is done when symptoms appear. CVS management can be done conservatively, endovascular intervention, and surgery. Conservative therapy that can be done is elevation of the extremities and administration of anticoagulants to prevent the occurrence of thrombosis. Conservative therapy is done to treat acute thrombosis, and is not useful in chronic thrombosis.5

Endovascular intervention is the main choice therapy for CVS. Treatment options according to KDOQI are percutaneous transluminal angioplasty, direct atherectomy during angioplasty, and placement of stents. Overall percutaneous transluminal angioplasty (PTA) has a success rate of 70-90%. PTA deficiency is low venous patency and restenosis often occurs so PTA must be repeated every three months. Therefore it is recommended to install stents. However, stents have disadvantages such as migration of stents and neointima intrastent hyperplasia

Indications for surgical therapy in the event of failure of endovascular therapy. Surgical therapy can include stenosis bypassing the area and vein anastomosis to the vein or vein to the right atrium.5 Management of CVS in terms of endovascular and surgery requires large costs.

Methodology

This research is an observational analytic study. The design of this study is a case control study. The variables studied were the duration of use of central venous catheters (CVC) and the frequency of placement of CVC as independent variables and central venous stenosis (CVS) as dependent variables. The data of this study were obtained from the medical records of patients in the Vascular Division of the Department of Surgery at RSCM.

The population of this study was stage 4-5 CRF patients who underwent a central venous catheter for hemodialysis access made by the Vascular Division of the Department of Surgery, FKUI-RSCM in the 2013 – 2015. Of the total population, a case group was selected (stage 4-5 CRF patients with CVC who have CVS) compared to the control group (stage 4–5 CRF patients with CVC who did not have CVS). The study sample was a population that met the inclusion criteria. Samples were taken from medical record data from patients treated in January 2013 - December 2015.

The sample size was calculated for each variable and a total sample

of 30 subjects were obtained, with a ratio of 1:4 between the case group and the control group. Total sample of 150 subjects, consisting of 30 subjects as case group and 120 subjects as control group.

The inclusion criteria were patients with the first insertion of short-term types CDL. The output studied was a comparative analysis between case groups and controls in terms of frequency, duration and location of central venous installation. Data collection was done through the patient's status in the medical record of the Vascular Division of RSCM Surgical Department and through interviews with subjects to reduce the risk of recall bias. Then from the status, data is being collected in the form of age, sex, location of central venous catheter installation for hemodialysis access, duration of use of central venous catheters, comorbid disease, patients who experience central venous stenosis after central venous catheter placement. The data obtained were processed with univariate analysis presented in the form of frequency distribution tables to show the characteristics of the subject of central venous stenosis. After that a bivariate analysis was conducted to determine the correlation between groups of subjects by determining the Odds ratio (OR). Data processing is done using the SPSS 20.0 program and with Chi Square test.

Results

Based on data registry from the Division of Vascular Surgery, Department of Surgery, FKUI-RSCM in 2013 – 2015, 717 subjects were found to have a central venous catheter for hemodialysis access, 54 subjects experienced central venous stenosis (incidence of 7.53%), 32 subjects who meet the inclusion criteria as a case group. (Table 4.1) Matching based on age (> 45 years) and sex (male) in accordance with the case group with a ratio of 1: 4 so that 128 subjects of CKD were carried out with a central venous catheter for hemodialysis access but did not experience CVS as control group.

Table 4.1 Incidence of central venous stenosis at RSCM 2013 – 2015

Variable	n	Percentage (%)
Central venous stenosis	54	7,53
No central venous stenosis	663	92,7
Total	717	100

In the comorbid disease group, 30 CVS subjects were found in hypertensive subjects (93.7%) and 108 subjects (84.3%) did not have CVS. Whereas in both groups with and without CVS, there were only 7 subjects with type 2 diabetes mellitus. In subjects with central venous access location in the subclavian vein, 28 subjects (59.6%) experienced CVS and 19 subjects (40, 4%) did not experience CVS. Whereas in subjects with location of central venous access in the internal jugular vein, 4 subjects (3.5%) experienced CVS and 109 subjects (96.5%) did not experience CVS. The location of the installation of a central venous catheter in the subclavian vein had a significant relationship with the occurrence of central venous stenosis with p <0.001 at a 95% confidence level. (Table 4.2)

Table 4.2 Demographic characteristics of CVS patients in CKD patients with central venous access at RSCM 2013 – 2015

Characteristics	n(%)		P
	Central Venous Stenosis	No Central Venous Stenosis	
Age Category <45 years >45 years	- 32	- 128	
Sex Male Female	32 -	128 -	
Comorbid Disease Diabetes Hypertension	0 (0%) 30 (93,7%)	7 (5,5%) 108 (84,3%)	
Location of central venous catheter for hemodialysis access Subclavian veins Internal jugular vein	28 (59,6%) 4 (3,5%)	19 (40,4%) 109 (96,5%)	<0,001

Based on the duration, as a factor associated with CVS in CKD patients with central venous access, CVS was found in 25 subjects (22.5%) with a catheter duration of > 6 weeks and in 7 subjects (13.7%) with catheter use duration < 6 weeks. CVS was not obtained in 84 subjects (77.5%) with a duration of catheter use > 6 weeks and 44 subjects (86.3%) with a catheter duration of < 6 weeks.

Based on the frequency of central venous catheter insertion, CVS occurred in 28 subjects (53.8%) with a frequency of central venous catheter insertion > 2 times and 4 subjects (4%) with a frequency of central venous catheter insertion < 2 times. CVS did not occur in 24 subjects (46.2%) with a frequency of central venous catheter insertion > 2 times and 104 subjects (96%) with a frequency of central venous catheter insertion < 2 times. (Table 4.3)

There was no significant relationship between catheter insertion duration (p = 0.207) and CVS occurrence at 95% confidence level. A significant association was found between the frequency of central venous catheter insertion and CVS (p <0.001) at 95% confidence level. Odds ratio values obtained at the frequency of catheter insertion > 2 times were 30 times compared to the frequency of catheter insertion < 2 times with a 95% confidence interval 9.7 - 95.6.

Table 4.3. Analysis of factors related to CVS occurrence in CKD patients with central venous access at RSCM 2013 – 2015

	Central venous stenosis n (%)	No stenosis of central vein n (%)	OR	Confidence Interval (CI) 95%	P
Duration of catheter use > 6 weeks <6 weeks	25(22,5%) 7 (13,7%)	84 (77,5%) 44 (86,3%)	1,9	0,8-4,7	0,207
Frequency of catheter insertion > 2 times <2 times	28 (53,8%) 4 (4%)	24 (46,2%) 104 (96%)	30	9,7-94,6	<0,001

Discussion

A well functioned permanent vascular access is needed to maintain smooth hemodialysis. Almost all guidelines in the community recommend arteriovenous fistulas as long-term access to hemodialysis because they have the least complications compared to arteriovenous graft and central venous catheters.1,8,14 The use of central venous catheters (CVC) as temporary vascular access is unavoidable, although the prevalence of venous stenosis or thrombosis reaches 10% to 50%.5 This is because many cases of emergency hemodialysis require immediate access. Minimizing the use of a central venous catheter (CVC) by making an arteriovenous fistula before CKD stage 5 is an important component in dealing with CVS. Most of the cases found in this study were patients who came in need of emergency hemodialysis so that the first access was installed in the form of a temporary CVC.

Veins that are included in the central veins are subclavian veins, brachiocephalic veins and superior vena cava. In the lower extremities, veins that included in the central veins are the iliac vein and inferior vena cava.8 Central venous stenosis (CVS) is defined as stenosis or occlusion of the subclavian vein or brachiocephalic vein

or superior vena cava.20 CVS interferes with the hemodialysis access circuit causing venous hypertension and access flow dysfunction with or without symptoms. This can cause loss of access due to access malfunctions or because of ligation done to eliminate symptoms. The diagnosis of CVS is based on a collection of symptoms and venographic findings. The most common symptom of CVS is swelling in the ipsilateral arm where the CVC, chest, neck and face are located. In addition, there is often an arteriovenous access dysfunction with decreased access flow. On physical examination can be found dilatation of collateral veins in the neck, chest and arms.5 Pathogenesis of CVS because CVC is trauma caused by the catheter in the endothelium and secondary inflammation in the vessel wall when insertion is performed. Another mechanism is the presence of a foreign body in the vein, accompanied by an increase in flow and turbulence in patients who have access to arteriovenous. Turbulence of blood flow causes an inflammatory response and stimulation of intimal hyperplasia.7,11,19 The symptoms most frequently complained of by the subjects in this study were arm edema (85%) which the swelling extended to the face (77.5%) with hemodialysis access that is unable to be used (44.7%), this is in accordance with the literature which reports the three CVS symptoms that are most frequently complained.[17]

In this study, the number of subjects obtained was 32 cases and 128 control groups with a ratio of 1: 4. Matching is based on age (> 45 years) and sex (male). Comorbid hypertension was found in 93.7% subjects with CVS and 84.3% in non CVS subjects. This is consistent with the literature which reports that more than 90% of subjects undergoing hemodialysis due to CKD suffer from hypertension. Only 5.5% of subjects suffering from diabetes mellitus in this study, whereas in the literature with Asian populations with CKD undergoing hemodialysis reported more than 60% had diabetes.20

In this study, there was a significant association between the frequency of inserting a central venous catheter and the occurrence of CVS. There is a 30-fold risk of CVS occurring in patients with central venous catheter placement > 2 times compared with those with < 2 times. This is consistent with the study of MacRae (2005) which states the incidence of CVS occurs in the installation of a central venous catheter > 1 times.12 Repeated placement of a central venous catheter triggers trauma to the venous wall. This trauma causes inflammatory processes, thrombus formation, and changes in venous wall histology. The body responds to the catheter as a foreign object causing an inflammatory reaction. Inflammatory reactions cause migration of smooth muscle cells to the intimal layer, causing smooth muscle proliferation and thickening of the venous wall. Repetitive frictions of the catheter against the venous wall and blood turbulence also cause thickening of the venous wall and platelet deposits. Veins that have lost vascular tone cause CVS.5,[9]

In this study there was no significant association between the duration of use of a central venous catheter and the occurrence of CVS. While the study by McRae (2005) stated that patients who experienced CVS had a longer duration of dialysis duration, which was 43 months compared to 34 months.7 This is consistent with the study of Hernandez (1998) who stated CVS is more common in longer usage, namely 49 days compared to 29 days.12 The pathogenesis of CVS in the longer duration of central venous catheter use is similar to pathogenesis at the frequency of repeated insertions. Structural changes in the venous wall last from 24 hours after endothelial denudation with platelet microtrombus formation. This response continues so that smooth muscle cells are layered in the injured area.5,9 Histological studies in the central vein after catheter placement by Forauer (2003) found that in short-term catheter use (<14 days) local intima injury occurred with denudation endothelium and attached thrombus layer. Whereas, for long-term catheter use (> 90 days), smooth muscle cell proliferation is found which causes thickening of the venous wall. The focal area of catheter placement in the venous wall consists of thrombus at various stages, collagen, and endothelial cells.[19]

Another risk factor that can cause CVS is the location of the installation of a central venous catheter, which is the subclavian vein, as well as the placement on the left side. Installation of the right internal jugular vein is the best choice because it has the least contact with the vessel wall. Whereas in the installation on the left side of the internal jugular vein, the catheter must go through a complex anatomical pathway, including angulation between the left internal jugular vein, brachiocephalica vein, and superior vena cava.12,17,20 In this study a significant relationship was found (p <0.001) between the installation of a central venous catheter in the subclavian vein (59.6%) with the occurrence of CVS, compared with internal jugular vein insertion (3.5%). This finding is also consistent with the previous literature.12,17,20

Conclusions

1. The frequency of inserting a central venous catheter > 2 times is a risk factor for central venous stenosis.
2. Duration of central venous catheter insertion > 6 weeks is not a risk factor for central venous stenosis.
3. Other risk factors associated with the occurrence of CVS are the location of the installation in subclavian vein.

Suggestions

1. Can be used as a guideline for the procedure for installing a central venous catheter at the RSCM.
a. Minimize the installation of a central venous catheter by making permanent vascular access before stage 5 chronic kidney failure.
b. In case of immediate access to emergency hemodialysis, avoid placing a central venous catheter in the subclavian vein.
2. Further research can be conducted regarding the relationship of other risk factors (side of installation, infection at the installation location and catheter material) with the occurrence of CVS.
3. Research can be done on the results of the intervention of central venous stenosis.
4. Multicentre research can be carried out with a larger number of samples.

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