Central Venous Catheter Related Stenosis and Thrombosis of Superior Vena Cava: An Update of Treatment Strategies

Santral Venöz Katetere Bağlı Stenoz ve Superior Vena Cava Trombozu: Tedavi Stratejilerinde Yeni Yaklaşımlar

ABSTRACT Intravenous access is becoming an increasingly important part of health care nowadays. These vascular access devices are ideal for infusion of toxic, viscous, and irritating substances such as chemotherapeutic agents, total parenteral nutrition, hemodialysis, antibiotics, repeated blood transfusions and repeated venesection. Due the fact that central venous stenosis can stay asymptomatic and routine venography and/or ultrasonography are not routine after central venous catheter placement or removal, the real incidence of central venous stenosis is uncertain and is likely to be underestimated. The high prevalence seen especially in dialysis patients perhaps reflects the fact that central venous stenosis becomes clinically manifest as the blood flow through the dialysis access decreases, leading to venous engorgement. The source of most of the currently available data is limited to the studies of symptomatic patients who required imaging studies. Superior vena cava syndrome is the clinical manifestation of partial or total obstruction of the superior vena cava and may presented in an emergency condition especially in patients with central venous catheters. Although it is rare, in the absence of sufficient collateral circulation, superior vena cava syndrome may cause hemodynamic deterioration with respiratory and cardiac arrest. The current study will focus on central venous catheter related stenosis and thrombosis, which is one of the major problem of these devices and moreover, prevention and treatment strategies of the major complication such as superior vena cava syndrome will be discussed.

Key Words: Catheterization, central venous; superior vena cava syndrome


Anahtar Kelimeler: Kateterizasyon, santral venöz kateter; superior vena kava sendromu

Intravenous (IV) access is becoming an increasingly important part of health care nowadays. Vascular access devices are ideal for infusion of toxic, viscous, and irritating substances such as chemotherapeutic agents, total parenteral nutrition, hemodialysis, antibiotics, repeated blood transfusions and repeated venesection, respectively. The need for a high safety profile, minimal untoward effects, cost containment, and enhanced patient satisfaction has facilitated the evolution of increasingly sophisticated catheter technology during the past 20 years. Although many variations exist, central venous access is usually established by some modalities such as subcutaneous catheters, totally implanted systems and peripherally inserted catheters. The function of the access will greatly determine the quality of life that this patient population will enjoy. In recent years in many institutions, these devices are replacing neck or chest wall central venous catheters (CVC) as the access of choice for intermediate and long-term intravenous therapy and offer a safe, efficient, and cost-effective alternative to surgically placed CVCs.

Superior vena cava syndrome (SVCS) is the clinical manifestation of partial or total obstruction of the superior vena cava and may presented in an emergency condition especially in patients with CVCs. The first known case report of SVCS that was related to syphilitic aneurysm of the ascending aorta published by William Hunter in 1757 but nowadays the reason of the disease shifted to malignant disorders in over the 80% of the cases. However, there has been an increase in the number of cases of SVCS associated with iatrogenic causes such as the placement of pacemaker wires and long-term central venous catheters in recent years.

Rapid onset of SVCS, in the absence of collateral circulation, may cause a more dramatic and life-threatening presentation, often with neurologic and respiratory sequelae resulting from cerebral and laryngeal edema. The current review will focus on one of the acute threatened complication such as superior vena cava syndrome associated with CVC and potential for prevention and treatment strategies in adult patients.

VASCULAR ACCESS DEVICES

Nowadays several types of vascular access devices are exist. Major types are:

1) The midline catheter is a type of IV line that is somewhat like a routine IV and a central catheter. It is placed through a vein near the elbow and threaded through a large vein in the upper arm. Though durable, at 4 to 6 inches, the midline catheter is not long enough to give some highly irritating medications.

2) The peripherally inserted central catheter (PICC) is also introduced through an arm vein but its tip lies in a large central vein. It typically provides central IV access for up to 4 to 8 weeks. A PICC may remain in place for 3 to 5 months in special cases, as long as it continues to work well and if it is not infected. However, it is still considered a temporary catheter. Imaging guidance - by fluoroscopy or ultrasound is sometimes necessary, in which case the PICC will be placed by a specially trained doctor or physician’s assistant in the imaging service department. Because a PICC can be cared for at home, patients can often go home from the hospital earlier than with other catheter placements. Any trained health care worker can easily pull the PICC line out when it is no longer needed.

3) The tunneled catheter, also known as a Hickman, Broviac, or Groshong catheter, is a permanent catheter that is fixed in place when scar tissue forms. It is typically inserted into the subclavian vein or into the external jugular vein. It is then tunneled from the puncture site down onto the chest wall, emerging from the skin about 6 inches from where it entered the vein. This type of catheter is the best choice when a patient is likely to need access for longer than 3 months and when the line will be used many times each day. It is secure and easy to use. A drawback of these catheters is that a small percentage of tunneled catheters must be removed prematurely due to infection.

4) The subcutaneous port is a permanent device made up of a catheter attached to a small basin implanted beneath the skin. The entire device is inside - nothing can be seen on the outside of the skin except for a small bulge. The catheter, which
passes from an access site in a vein of the arm, shoulder, or neck, ends in a large central vein in the chest. The basin has a silicone covering that can be punctured with a special needle. The port is used mainly when IV access is needed every so often over a long period, as in chemotherapy. Its only drawback is the need for a needle stick whenever treatment is given, but discomfort usually is not marked and tends to decrease over time. All types of CVCs were summarized at Table 1.

### COMPLICATIONS

There are numerous complications associated with the use of CVCs. Among those, procedural ones appear during the early phase, along with significant changes in the clinical picture of patients; therefore, they can be easily recognized. Minor procedural complications include failed venous puncture and catheter malposition. Major procedural complications include hematoma, hemopneumothorax, air embolism, and arterial or neural injury. Post-procedural complications include infectious and thrombotic complications, catheter kink, migration, “pinch off” syndrome, catheter rupture, and cardiac complications.10

### INCIDENCE OF STENOSIS AND THROMBOSIS

Due the fact that central venous stenosis (CVS) can stay asymptomatic and routine venograms are not usual after CVC placement or removal, the incidence of CVS is uncertain and is likely to be underestimated. The high prevalence seen especially in dialysis patients perhaps reflects the fact that CVS only becomes clinically manifest as the blood flow through the maturing dialysis access increases, leading to venous engorgement because of poor outflow. Thus, the source of most of the currently available data is limited to the studies of symptomatic patients who required imaging studies. In previous studies, the incidence of venous thrombosis following PICC or port placement has been reported to be between approximately 2% and 66%.11-29 The wide range in observed incidence may be partly caused by different diagnostic modalities (venography, ultrasound), the used criteria, and patient- and CVC characteristics. For the purpose of this review these studies were selected and summarized in Table 2, according to the indication for the CVC, i.e. the underlying disease and the type of thrombosis (subclinical, clinically manifest and overall).

### RISK FACTORS FOR THROMBOSIS

The mechanism behind intravascular thrombosis in these kinds of devices is best explained by Virchow’s theory of thrombotic pathogenesis, which postulates that intravascular thrombosis is caused by endothelial damage due to local trauma or inflammation of the vessel wall, stasis of blood flow and hypercoagulable states. All three mechanisms of acute thrombus formation may apply to indwelling intravenous catheters.30

Compression of the vein by an external mass can produce symptoms and should be excluded. In many studies, SVCS associated with bronchogenic carcinoma and lymphoma is well-described.31

It is relatively rare for CVS to occur in the absence of previous venous catheterization. Multiple CVC placements and longer catheter dwell times have been associated with a higher risk of CVS. In case of subclavian vein stenosis, the mean number of ipsilateral catheters was 1.6 with mean duration of 5.5 weeks.32-34 Longer dwell time of CVC increases the duration of wall injury. Patients with persistent stenosis at 6 months had a greater number of inserted catheters, longer time in place (49 days vs. 29 days), more dialysis sessions, and more catheter related infections than those who recanalized spontaneously. Though CVS is not as common with short term catheters, these catheters are not completely benign.35,36

Pericatheter sleeves, thrombus formation, and brachiocephalic vein stenoses have all been reported with catheters that had been in place on av-

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**TABLE 1: Types of central venous catheters.**

<table>
<thead>
<tr>
<th>1) Short Term devices (a day-2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Percutaneous internal jugular, subclavian, femoral lines</td>
</tr>
<tr>
<td>- Peripherally inserted central catheters</td>
</tr>
<tr>
<td>2) Long Term devices (2 weeks-years)</td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>- Totally implanted venous catheters</td>
</tr>
<tr>
<td>- Tunneled catheters (Hickman, Groshong, Broviac, Quinton)</td>
</tr>
</tbody>
</table>

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**TABLE 2: Incidence of venous thrombosis following PICC or port placement.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Thrombosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>Subclinical</td>
<td>2%</td>
</tr>
<tr>
<td>Study 2</td>
<td>Clinically manifest</td>
<td>66%</td>
</tr>
<tr>
<td>Study 3</td>
<td>Overall</td>
<td>49%</td>
</tr>
</tbody>
</table>

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Ahmet Ümit GÜLLÜ ve ark. SANTRAL VENÖZ KATETERE BAĞLI STENOZ VE SUPERİOR VENA CAVA TROMBOZU...
average of 21 days. Location of CVC is an important factor in causation of CVS.34–36

Large scale, prospective, observational studies performed at tertiary cancer centers demonstrated a lower incidence of thrombosis when the CVC were inserted in the internal jugular vein (0.6%) compared to the subclavian vein (2%).37 There is a predilection for CVS to occur with left sided catheter placement, this is probably a reflection of the anatomy of the upper venous system. Catheter flow problems, infection, and central vein obstruction were significantly more common with left sided catheters in a study of 294 patients with 403 right and 77 left IJ catheterizations.38–40

Catheter infections can be associated with the development of CVS, especially with subclavian vein catheterization. In a study of patients with subclavian catheters, those with persistent venous stenosis 6 months after removal of the catheter had more catheter insertions and catheter related infections.41,42

Although in some of studies no relation is found between catheter size and venous abnormalities in some others show a linear relationship between catheter size and venous thrombosis rates in smaller diameter catheters - 1% with 4-F, 6.6% with 5-F, and 9.8% with 6-F catheters in upper arm veins.12

Recent recognition of CVS associated with PICC lines and pacemaker wires is also concerning. As the number and use of such catheters is increasing tremendously for various reasons, this may become an important cause of CVS in patients needing vascular access for hemodialysis in the future. Many complications of CVC may be related to the position of the catheter tip, which has traditionally been placed in the central part of SVC or at the cavoatrial junction.43 It has now become common to place the tip of the dialysis catheter in the lower part of the right atrium for better performance, although it may occasionally be complicated by intraatrial thrombus. More CVC movement with the cardiac cycle when the

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>No of Patients</th>
<th>Reason for Catheter Placement</th>
<th>Entry site of CVC</th>
<th>Imaging Technique (U/V)</th>
<th>Objective thrombus formation (%) / Symptomatic (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timsit et al. (1998)</td>
<td>208</td>
<td>Feeding at ICU &amp; subclavian vein</td>
<td>U</td>
<td>33/0</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Wu et al. (1999)</td>
<td>81</td>
<td>Feeding at ICU</td>
<td>Jugular vein</td>
<td>U</td>
<td>56/0</td>
<td>15</td>
</tr>
<tr>
<td>Martin et al. (1999)</td>
<td>60</td>
<td>Feeding at ICU</td>
<td>Subclavian vein</td>
<td>U</td>
<td>58/2</td>
<td>16</td>
</tr>
<tr>
<td>Goto et al. (1998)</td>
<td>100</td>
<td>Feeding at ICU</td>
<td>Cephalic &amp; subclavian vein</td>
<td>V</td>
<td>23/0</td>
<td>17</td>
</tr>
<tr>
<td>Lin et al. (1999)</td>
<td>109</td>
<td>Feeding at ICU</td>
<td>Cephalic &amp; subclavian vein</td>
<td>U</td>
<td>6/0</td>
<td>18</td>
</tr>
<tr>
<td>Van Rooden et al. (2004)</td>
<td>145</td>
<td>Feeding at ICU</td>
<td>Cephalic &amp; subclavian vein</td>
<td>U</td>
<td>23/2</td>
<td>19</td>
</tr>
<tr>
<td>Balestri et al. (1995)</td>
<td>57</td>
<td>Feeding at ICU</td>
<td>Subclavian vein</td>
<td>V</td>
<td>56/0</td>
<td>20</td>
</tr>
<tr>
<td>De Cicco et al. (1997)</td>
<td>95</td>
<td>Feeding at ICU</td>
<td>Subclavian vein</td>
<td>V</td>
<td>66/6</td>
<td>21</td>
</tr>
<tr>
<td>Biffi et al. (2001)</td>
<td>302</td>
<td>Feeding at ICU</td>
<td>Subclavian &amp; cephalic vein</td>
<td>U</td>
<td>4/2</td>
<td>22</td>
</tr>
<tr>
<td>Luciani et al. (2001)</td>
<td>145</td>
<td>Feeding at ICU</td>
<td>Subclavian vein</td>
<td>U</td>
<td>12/3</td>
<td>23</td>
</tr>
<tr>
<td>Harter et al. (2002)</td>
<td>233</td>
<td>Feeding at ICU</td>
<td>Jugular vein</td>
<td>U</td>
<td>2/0</td>
<td>24</td>
</tr>
<tr>
<td>Van Rooden et al. (2003)</td>
<td>105</td>
<td>Feeding at ICU</td>
<td>Jugular &amp; subclavian vein</td>
<td>U</td>
<td>28/12</td>
<td>25</td>
</tr>
<tr>
<td>Couban et al. (2005)</td>
<td>255</td>
<td>Feeding at ICU</td>
<td>Jugular &amp; subclavian vein</td>
<td>U</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Verso et al. (2005)</td>
<td>385</td>
<td>Feeding at ICU &amp; subclavian vein</td>
<td>V</td>
<td>18/2</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Wilkin et al. (2003)</td>
<td>143</td>
<td>Feeding at ICU</td>
<td>Hemodialysis</td>
<td>D</td>
<td>26/not reported</td>
<td>28</td>
</tr>
<tr>
<td>Trerotola et al. (2000)</td>
<td>238</td>
<td>Feeding at ICU</td>
<td>Malignancy+</td>
<td>U+V</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>

ICU: Intensity care unit; U: Ultrasonography; V: Venography.
tip is within the heart may predispose to CVS. However, a short catheter, especially if placed from the left-hand side with close approximation of its tip to the wall of SVC, is especially likely to result in endothelial damage and inflammatory response, which, over the long term, may lead to CVS. The vessel wall may respond variably to different catheter materials - a concept related to stiffness and presumed “biocompatibility” of the polymer. In a rabbit model, polyethylene and Teflon catheters were associated with more inflammation than was seen with catheters composed of silicon and polyurethane; the stiff nature of polyethylene and Teflon was considered etiologic. In addition, silicone dialysis catheters were associated with a lower incidence of CVS than were polyurethane catheters.44-46

Although patients with malignancy have a sevenfold risk of thrombosis compared to patients without malignancy, difference in CVC-associated thrombosis among patients with different types of tumors did not observed in many multicenter and randomized studies.26,47-48

The role of thrombophilic mutations in promoting CVS is unclear but a recent meta-analysis of 10 studies with 1,000 patients reported that the pooled odds ratio for catheter related thrombosis was 4.6 in patients with factor V Leiden and 4.9 for the prothrombin gene mutation.49

PROPHYLAXIS FOR CATHETER-RELATED DEEP VENOUS THROMBOSIS

Prophylactic anticoagulation for patients with CVC has been studied for more than two decades and resulted with varying results. These studies include heterogeneous populations of patients with different types of vascular access devices inserted in different central veins. Multiple anticoagulants have been studied for varying duration, and the study endpoints have varied greatly from study to study. Moreover, the reports also have utilized different imaging modalities to establish venous thrombosis. In a recent meta-analysis including seven randomized controlled trials, the use of low molecular weight heparin in cancer patients with CVC was associated with a trend towards a reduction in symptomatic DVT but the data did not show any statistically significant effect on mortality, infection, major bleeding. The effect of warfarin on symptomatic DVT was not statistically significant in this meta-analysis.50

SUPERIOR VENA CAVA SYNDROME

The triad of facial plethora, venous distention, and isolated upper hemibody edema is sufficient for a diagnosis of SVCS, which is defined as the clinical manifestation of partial or total obstruction of the superior vena cava.5

The development of clinical manifestations of SVCS depends on the amount of venous hypertension, the delay in circulation time, the development of collateral pathways of circulation, and the clinical signs and symptoms of the underlying causative pathophysiologic process. In the absence of sufficient collateral circulation may cause hemodynamic deterioration and the patient may suffer respiratory and cardiac arrest.51

Superior vena cava syndrome is a clinical diagnosis, and an underlying pathology must be determined. Roughly, 80% of cases of SVCS are secondary to bronchogenic carcinoma, with small cell carcinoma of the lung accounting for a disproportionate fraction.5 Malignant lymphoma, miscellaneous malignancies, and benign causes account for the remaining 20% of cases. However, the increased current use of invasive monitoring and therapeutic interventions such as central lines, cardiac pacemakers, permanent port accesses for chemotherapy application, catheters for total parenteral nutrition and Swan-Ganz monitoring devices, is associated with increasing reports of thrombosis of superior vena cava.52,53

TREATMENT STRATEGIES

SVCS requires prompt diagnosis and therapy. Therapies that address the existing thrombus include supportive care, anticoagulation, thrombolysis, transcatheter recanalization and subsequent balloon dilatation, intravascular stenting, local pharmacomechanical thrombolysis, and surgery.54-56 In addition to these treatment modalities, combination chemotherapy and radiation therapies have
long been the main stay of the treatment of choice for mediastinal tumors causing SVCS.

There are several surgical by-pass techniques with autograft or synthetic grafts described for the reconstruction of SVC but these interventions remains controversial. Spiral vein by-pass grafting reported by Doty et al. is described as wrapping of the vein graft in spiral fashion around a stent of appropriate diameter. Then the edges of the vein are continuously suture to create a large-diameter conduit. Their data show that by-pass of the obstructed SVC with this technique relieves superior vena caval syndrome and demonstrate long-term patency of the graft such as 15 years. Niederle et al. reported three patients with SVCS caused by tumor thrombus. Two patients were clinically asymptomatic after surgical treatment but unfortunately, one of the other patients who were undergone to SVC reconstruction with a PTFE graft was occluded three months later. Thus, aggressive surgery may be useful to relieve SVCS. However, Hasegawa et al. reported immediate occurrence of intrapulmonary spread of the tumor after surgery with cardiopulmonary bypass, resulting in perioperative mortality due to respiratory failure.

A thrombus can sometimes be relatively easily removed by thrombectomy from the brachiocephalic vein under cardiopulmonary by-pass in selected patients. Koike and Yamagami had reported successful results with this technique in patients with malign diseases.

The use of intravascular stents used for both malignant and benign causes of SVCS has become an important therapeutic option for this disease. The optimal timing of stent placement is still controversial, although recent literature supports the safety and effectiveness of stenting as primary treatment for SVCS. Stenting provides the most rapid alleviation of symptoms while allowing the patient to continue with other treatment such as radiotherapy or chemotherapy if needed. Complete resolution of the SVCS occurs in 68% to 100% of patients treated with metallic stents. Catheter-directed thrombolysis is often used in conjunction with stent placement and anticoagulation is frequently recommended.

Catheter-directed thrombolysis is particularly appealing because it is effective in achieving patency of the lumen and removal of thrombus lining the venous valves. Nowadays, three choices exist for thrombolytic therapy: Streptokinase, urokinase and tissue plasminogen activator (t-PA). Streptokinase activates the fibrinolytic system through the cleavage of plasminogen molecule and formation of plasmin. The inherent disadvantage is that streptokinase exhibits no fibrin selectivity, clearing both systemic and thrombus associated fibrin and fibrinogen. An additionally concern is that most of patients especially children, may produce antibodies directed against streptokinase due to immune response from previous beta hemolytic streptococcal infections, thereby increasing the incidence of allergic reactions.

Urokinase is a human protein primarily produced by renal and vascular endothelial cells. It acts directly as an enzyme to produce plasmin from plasminogen in both the plasma and the site of the thrombus, thus producing the 'lytic' state. An advantage of urokinase is that it is not a foreign protein, such as streptokinase and antibodies are therefore not produced against it.

t-PA is a fibrin-specific, recombinant form of the mammalian protease tissue plasminogen activator, produced by inserting the human tissue plasminogen activator gene into the ovarian cell line and has potential advantages over the first-generation plasminogen activators, streptokinase and urokinase. Indeed, t-PA has a higher affinity for fibrin and is activated by fibrin, which enables it to activate plasminogen on the fibrin surface. Because of this fibrin specificity, t-PA has the potential to induce effective thrombolysis without producing systemic plasma proteolysis.

It is important to remember that patients with SVCS are at increased risk for recurrent DVT and pulmonary embolism and, therefore, should receive anticoagulation after either successful or unsuccessful thrombolytic therapy. Likewise, with symptom resolution and catheter preservation after thrombolytic therapy, anticoagulation should be maintained as long as the catheter is present.
CONCLUSION

Today, intravenous (IV) access is becoming an increasingly important part of health care. Even stays symptom free in usual, catheter-related thrombosis is a common clinical problem that may affect many patients with central venous catheters. Cancer patients with CVC considering anticoagulation, should consider the possible benefit of reduced incidence of thromboembolic complications against the burden and harms of anticoagulation. Physicians' compliance for primary prevention of venous thromboembolism should be implemented in patients considered at high risk of venous thromboembolism such as metastatic cancer, presence of long-term central venous catheters and infusional chemotherapy. Factor V Leiden carriers, identified among cancer patients who had a positive history of venous thromboembolism are likely to benefit from an antithrombotic prophylaxis. While recently published guidelines might help standardize the therapy, future prospective controlled studies should be adequately powered and evaluate the effects of newer anticoagulants and other treatment modalities in cancer patients with CVC.

REFERENCES