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REVIEW ARTICLE

Current perspective of venous thrombosis in the upper extremity

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See also Watson HG. Upper extremity deep vein thrombosis – not the same disease at a different site. This issue, pp 1267–8; Lechner D, Wiener C, Weltermann A, Eischer L, Eichinger S, Kyrle PA. Comparison between idiopathic deep vein thrombosis of the upper and lower extremity regarding risk factors and recurrence. This issue, pp 1269–74.

Summary. Venous thrombosis of the upper extremity is a rare disease. Therefore, not as much is known about risk factors, treatment and the risk of recurrence as for venous thrombosis of the leg. Only central venous catheters and strenuous exercise are commonly known risk factors for an upper extremity venous thrombosis. In this review an overview of the different risk factors, possible treatments and the complications for patients with a venous thrombosis of the upper extremity is given.

Keywords: upper extremity, venous thrombosis.

Introduction

Venous thrombosis of the upper extremity (UEDVT), defined as a thrombus in the subclavian, axillary or brachial vein, accounts for 4–10% of all venous thromboses [1–6]. This figure may be an underestimation given that UEDVT is often asymptomatic [7–9]. The low incidence of UEDVT compared with the leg may be explained by the lower gravitational stress. Additionally, the veins of the upper extremities contain fewer valves than the legs, which could be potential foci for thrombus formation. Furthermore, stasis contributing to the occurrence of thrombosis is very rare in the upper extremity. The most likely conditions for stasis to occur are surgery and plaster cast of the upper extremity [7,10].

Primary venous thrombosis

UEDVT is usually divided into primary and secondary thrombosis [4,11]. Primary UEDVT includes idiopathic thrombosis and thrombosis associated with the thoracic outlet syndrome or effort (Paget–Schrötter syndrome) [12,13]. The incidence of primary UEDVT is 2 per 100 000 person years [2,14] and accounts for approximately 30% of all UEDVT[4,14,15].

Thoracic outlet syndrome (TOS) relates to various forms of compression in the thoracic outlet. The thoracic outlet is located between the base of the neck and the axilla. Compression of the thoracic outlet can either be on the brachial plexus or on the blood vessels in the outlet. Compression of both nerves and vessels is rare. In approximately 3–10% of the cases, TOS will be vascular, which can be divided into venous or arterial TOS [16]. UEDVT can be caused by venous TOS. In venous TOS the thoracic outlet veins are compressed by the clavicle and the first rib [17]. This will result in compression or sudden occlusion of the vein. Approximately 60% of patients with primary UEDVT have the thoracic outlet syndrome [4]. Treatment consists of either anticoagulation alone or in combination with resection of the first rib [17,18].

Paget–Schrötter syndrome, also called effort thrombosis, is a manifestation of TOS. The syndrome mostly occurs in young healthy persons, related to strenuous activity of the arm during sports [19–23]. The effort causes microtrauma of the vessel intima by repeated compression of the clavicle and first rib, which activates the coagulation [2]. The compression is mostly caused by trauma or by the enlarged muscles in the shoulder girdle [4,16,18,20,24–26].

Secondary venous thrombosis

Secondary UEDVT is thrombosis with a known risk factor. These risk factors can be genetic or acquired [11,27,28].

Central venous catheters

The main risk factor for UEDVT is a central venous catheter(CVC) [6,27]. The catheters are used to provide chemotherapy, medication and parenteral nutrition, and for administration of fluids, blood products and hemodialysis [9].

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Several studies have investigated the incidence and risk factors for UEDVT in patients with a CVC, as well as prophylaxis to prevent thrombosis [29–37].

CVCs can be divided into peripherally inserted catheters, chest catheters and pacemakers. Peripherally inserted catheters have an incidence of thrombosis from 10% to 38% [29,30,37]. The incidence of UEDVT for chest catheters ranges from 2% to 41% [31,32,35,37]. The risk of thrombosis is dependent on the diameter of the catheter; a larger diameter gives a higher risk of thrombosis [30]. The risk of UEDVT is lower for polyurethane and silicone catheters compared with polyethylene or Teflon-coated catheters [38,39].

Pacemakers give thrombosis in 10%. This risk increases with the number of leads from the pacemaker [40,41]. Most occlusions occur within the first 2 months after insertion of the catheter [30,42,43].

Malignancy

Malignancy is an important risk factor for UEDVT. However, the increased risk in patients with malignancy is mainly induced by CVCs [27,44,45]. In the Multiple Environmental and Genetic Assessment (MEGA) study of risk factors for venous thrombosis, a population-based case control study, 179 patients with UEDVT were compared with 2399 control subjects. In patients without a CVC with an active form of malignancy an 18-fold increased risk of UEDVT compared with patients without active malignancy was found. Active malignancy was defined as malignancy diagnosed 5 years or less before first venous thrombosis [27]. A 7.7-fold increased risk of UEDVT was found when all, active and inactive, malignancies were included.

Coagulation abnormalities and genetic risk factors

In the literature the prevalence of coagulation abnormalities in patients with UEDVT ranges from 8% to 61% [1,28,46–48]. The differences can be explained by the size of these studies, including only between 18 and 51 patients. Additionally, the studies had different time points of blood collection: at diagnosis of thrombosis, 3 weeks after the event or after discontinuation of anticoagulation therapy. This can influence the assessment of coagulation abnormalities. Only antiphospolipid antibodies seem consistently more frequently present compared with the healthy population [46–48].

Factor (F) V Leiden [49] and the prothrombin 20210A [50] mutation are common genetic risk factors in venous thrombosis of the leg, and may be a risk factor for UEDVT. Some studies reported an increased risk for either factor V Leiden or the prothrombin 20210A mutation or both. An Italian study included 115 patients with an UEDVT and 797 control subjects. A 5- to 6-fold increased risk of UEDVT was found for patients with one of the mutations [51]. In a Spanish study of 79 cases and 165 controls an increased risk was found for patients with the prothrombin 20210A mutation, and no effect was found for the FV Leiden mutation [11]. A follow-up study including 257 patients with a CVC found a 3-fold increased risk of a UEDVT in patients with a mutation compared with patients without a mutation [34]. Although the majority of the other studies showed an increased risk for patients with the FV Leiden or prothrombin 20210A mutation, the number of patients in these studies was small. Therefore, no solid conclusions can be drawn.

Oral contraceptive use, surgery and plaster cast

Oral contraceptive use did not increase the risk of UEDVT in most studies [4,46,51,52]. However, in a Spanish study a 5.7-fold (CI 2.1–15.7) increased risk was found, and the MEGA study found a 2-fold (CI 1.1–3.8) increased risk [11,27]. So, there is no consensus about oral contraceptive use as risk factor for UEDVT. Differences may be explained by the type of patients included in the studies. A study including patients with a primary UEDVT showed an increased risk while studies including patients with secondary UEDVT did not show an effect of oral contraceptives.

Surgery and plaster cast of the upper extremity result in stasis in the upper extremity. Only one study investigated surgery and plaster cast as a risk factor for UEDVT. This study found surgery of the upper extremity as a risk factor with an odds ratio of 13.1 (95% CI 2.1–80.6) [27]. Plaster cast of the arm increased the risk, with an odds ratio of 7.0 (95% CI 1.7–29.5) [27].

Other risk factors

Other possible risk factors for UEDVT are obesity, hormone replacement therapy (HRT) and pregnancy. Few studies have investigated these risk factors. Obesity and HRT were not risk factors [27,53]. A case series reported pregnancy, especially in combination with ovary hyperstimulation syndrome, as a risk factor in women for UEDVT [54]. However, no large studies were performed to assess the thrombotic risk for pregnancy.

Treatment

Unfortunately, no randomized controlled trials have been performed on the optimal treatment for patients with UEDVT. Therefore, there is still debate about what the best therapy is and how side-effects can be minimized. Anticoagulation is the most common treatment, with a similar strategy as for deep vein thrombosis of the leg consisting of low molecular weight heparin and vitamin K antagonists. Removal of the main risk factor, for instance a CVC, probably reduces the risk of a recurrent event. However, in most cases removal of the CVC is not possible and therefore it is inserted in the other arm or on the opposite side of the chest. Thrombolysis, surgery, thrombectomy and balloon dilatation with and without stent placing are used far less [55–59]. In these cases removal of a rib or correction of malformations of the ribs or clavicle may be part of the treatment. However, these aggressive forms of treatment may have serious side-effects. Thrombolysis gives a higher risk

Table 1 Overview of different studies regarding complications in patients with venous thrombosis of the upper extremity

Author	No. cases	% men	Mean age (range)	Primary vs. Secondary	PTS (%)	Recurrence (annual, %)	Mortality (%)
Hingorani 1997[15]	170	39	68 (9–101)	Both	7	–	34
Prandoni 1997[46]	27	70	53 (19–79)	Both	15	7	15
Martinelli 2004[51]	96	36	32 (14–61)	Primary	–	2	–
Baarslag 2004[67]	50	42	52 (23–86)	Both	18	8	50
Prandoni 2004[69]	53	31	44 –	Both	20	2	20
Hingorani 2005[66]	546	40	68 (1–101)	Both	–	–	29
Kahn 2005[68]	34	46	51 (22–86)	Both	44	–	–
Hingorani 2006[65]	598	38	69 (9–101)	Both	–	–	29

of bleeding and surgery can cause pneumothorax, nerve damage and rethrombosis [57,60]. Balloon thrombectomy and venous stents can cause thrombosis by inducing intima damage [59]. In several pilot studies thrombolysis was compared with standard anticoagulation therapy in patients with a UEDVT. Most patients reacted well to thrombolysis and there were only a few more bleedings compared with the standard treatment [61–63]. A clear advantage of thrombolytic therapy has not been shown. Recently, the outcomes of the RIETE registry of patients with venous thrombosis showed no difference in outcome after 3 months of therapy in patients with a deep vein thrombosis of the upper extremity or of the leg [64]. However, in this study treatment for UEDVT was different from that for thrombosis of the leg. Approximately 50% of the patients with UEDVT were only treated with low molecular weight heparins for 3 months and the other half with vitamin K antagonists. In venous thrombosis of the leg 70% of patients were treated with vitamin K antagonists. Therefore, the groups in this registry were not entirely comparable. These results show that patients with UEDVT with their current treatment have the same prognosis after 3 months as patients with venous thrombosis of the leg. Whether this is the most optimal treatment remains unclear.

Complications

The main complications of UEDVT are pulmonary emboli (30%), post-thrombotic syndrome (PTS) and death [15,46,65–67]. PTS occurs in 7–44% of patients [15,68,69] (Table 1). These percentages are based on small studies with different definitions of PTS. Mortality ranges from 15% to 50%, and is high because of major co-morbidity (e.g. malignancy, infection and multi-organ failure) [4,67,69].

In a few small studies the annual recurrence rate after a first UEDVT was 2% to 8%. However, groups were small and only one study found thrombophilia to be a possible risk factor for a recurrence; the other studies were too small to identify risk factors [51,67,69].

Conclusion

UEDVT is a rare disease that mainly occurs in patients with a CVC. Most other risk factors are the same as for patients with a venous thrombosis of the leg. Mortality, pulmonary embolism and PTS are the most important complications of UEDVT but the incidences of these complications vary between studies. The optimal treatment of UEDVT remains unclear.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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