Conventional treatment of proximal deep venous thrombosis: still a good choice?

Tratamento convencional da trombose venosa profunda proximal: ainda uma boa opção?

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The objectives of treatment for deep venous thrombosis (DVT) are to prevent pulmonary embolism, postthrombotic syndrome and recurrence of DVT. Several different types of treatments are available in the therapeutic arsenal to achieve these goals.[1]

The traditional initial conservative treatment is to administer unfractionated heparin (UFH) or low molecular weight heparin (LMWH), followed by warfarin (vitamin K antagonist, VKA) over the long term. Another treatment option, in particular for more serious cases with a greater extent of involvement, is fibrinolytic treatment (alteplase/Actilyse®), followed by anticoagulants. An alternative approach to these cases is venous thrombectomy with a Fogarty catheter followed by anticoagulants. More recently, pentasaccharide and a series of new anticoagulants, originally known as "new oral anticoagulants" (NOACs), which was later changed to "direct oral anticoagulants" (DOACs), have passed testing and are gradually being adopted for treatment of DVT and pulmonary embolism.

Evaluation of the indications for these treatments must take into account the relationships between their efficacy and safety, on the basis of their cost. Vascular surgeons are very familiar with venous thrombectomy, which is a treatment that became more widespread after the Fogarty catheter was introduced in 1963. Qvarfordt et al.[2] conducted a study that detected a significant reduction in intramuscular pressure soon after iliofemoral thrombectomy. In a recent review, Eklof[3] described the discouraging results achieved in the 1960s and how these improved with the introduction of technical improvements, such as construction of an adjuvant arteriovenous fistula. The 2016 consensus published by the American College of Chest Physicians (ACCP) emphasizes the lack of randomized studies and recommends anticoagulant treatment rather than thrombectomy (with an evidence level of 2C).[4] Given the invasivity of the procedure and the lack of evidence, this option is chosen rarely.

On the other hand, fibrinolysis has gained greater acceptance over the years. A Cochrane Library systematic review that was conducted by Watson et al.,[5] analyzing publications from 1969 to 2013, compared systemic, local or catheter-delivered fibrinolysis with conservative treatment in 1,103 patients. Complete lysis of the thrombus took place in 48.2% of the cases treated with fibrinolytics, compared with 27.2% of patients managed with conservative treatment. However, postthrombotic syndrome occurred in 42.9% and 64%, respectively, which is not a very large difference, bearing in mind the risks of bleeding and the costs involved in fibrinolysis. In a study focusing on a more recent technique in which the fibrinolytic agent is administered locally via a catheter, Bashir et al.[6] found that in 3,649 patients treated with fibrinolytics hospital stay was 40% longer and hospital costs were three times greater compared with conservative treatment. Additionally, treatment with fibrinolytics was associated with significantly more frequent complications, such as pulmonary embolism, intracranial hemorrhages and hematoma. Bearing in mind the costs and the serious complications, not to mention exposure to X-rays and contrast, fibrinolysis should be considered with caution as a possible treatment for this disease.

The DOAC group of drugs has been approved for use more recently. Their major advantages are oral administration, avoiding the need for laboratory tests for control, and their synthetic production process. Disadvantages are cost and the lack of antidotes. A systematic review published by Robertson et al.[7] reported results that were favorable to anti-Xa type NOACs when compared with conventional treatment, in terms of recurrence of DVT during the first 3 months after treatment, although results after 3 months were similar. Recurrence of DVT after treatment with anti-IIa type DOAC (dabigatran) was similar over time. In general, DOACs had better results for bleeding. As such, DOACs are effective and safe synthetic drugs, but costs are still higher and

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there are no antidotes. Additionally, they cannot be used with children, adolescents or pregnant women.

The limitations of heparin are parenteral administration, the need for control laboratory tests, the possibility of induced thrombocytopenia, osteoporosis with prolonged use and alopecia.[8] Additionally, it is a drug of animal origin, which can lead to risk of contamination by germs or undesirable substances. For example, in 2008 the process used in China for obtaining the raw material from pig intestines led to contamination of heparin used all over the world with dermatan sulfate, causing serious hemorrhagic complications in patients.[9]

Warfarin is a drug that is obtained from a plant called "sweet clover" and it was originally used as a rat poison. Its clinical application as an oral anticoagulant dates from 1954. This drug has several limitations, such as its delayed onset of action, a narrow therapeutic window and a wide range of drug interactions.[10] However, it offers efficacy for long-term treatment with a low rate of complications[11] and is inexpensive.

Low molecular weight heparin appeared in the 1980s, the fruit of pioneering studies conducted by Prof. Carl P. Dietrich of the Escola Paulista de Medicina.[12] It offers the advantages of a more predictable dose-response profile, without a need for monitoring, and a subcutaneous administration route, enabling home use.[13] However, the production process is biological, starting from UFH. It is very well-established and effective and it is used as standard when testing other anticoagulant drugs.

Pentasaccharide was released at the end of the last century. It is a synthetic drug which, as its name suggests, only contains the five saccarides from heparin and LMWH that are responsible for the bond with antithrombin. This medication (fondaparinux) is given parenterally via a subcutaneous route, in common with LMWH, and it has been rigorously tested and compared with LMWH for prevention and treatment of DVT, exhibiting similar levels of efficacy and safety.[14] When it was launched it was very expensive, but as time has passed the price has fallen to a level at which it is competitive with LMWH.

A 2016 consensus[4] published by the ACCP suggests using DOACs for initial treatment of DVT in patients who do not have cancer, using LMWH and VKA as alternatives when this is not possible. For patients with cancer, the recommendation is to use LMWH and VKA for long-term treatment (3 months). The recommendation is also to prefer anticoagulant treatment over thrombolysis by catheter and to substitute treatment with DOACs for management with LMWH and VKA in cases of DVT recurrence.

In view of the above, is there still a place for indicating conservative treatment? The answer is yes, since it is a safe and effective approach that has proven its worth through use over time and is inexpensive. Furthermore, it is particularly indicated for patients with renal failure, children and adolescents, patients with cancer, pregnant women and after venous thrombectomies and administration of fibrinolytics. Conservative treatment can be chosen in cases in which DVT progresses or recurs or in which there are impediments to use of other anticoagulant drugs, in cases with intense localized symptoms and in cases of planned surgery.

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