EDITORIAL

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Future prospects for prophylactic and therapeutic management of venous thrombosis: antithrombotic substances with lower risk of hemorrhage?

Perspectivas futuras na abordagem profilática e terapêutica da trombose venosa: substâncias antitrombóticas com menor risco hemorrágico?

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Anticoagulants are medications that have been essential for treatment and prophylaxis of venous thromboembolism since the 1940s, initially with heparins and vitamin K antagonists. However, even with the introduction of low molecular weight heparins, fondaparinux, and, more recently, direct oral anticoagulants, there is still a non-negligible risk of significant and even lethal hemorrhages.[1-4]

Knowledge that has been accumulated over recent decades, primarily from experimental studies, suggests that the immune system and inflammatory cells play a role in initial and localized activation of coagulation in the veins, triggering thrombosis, primarily in situations in which blood flow is reduced or blocked.[5-8] This state of stasis can occur in human beings in cases of venous compression and restriction to bed because of clinical diseases or surgery and also during anesthesia, immobilization due to trauma, paralysis, and long journeys.[9-11]

Studies in experimental models of thrombosis, provoked by reducing or halting blood flow by induced stenosis or ligature in the vena cava of rodents suggest that, in response to ischemia and activation of endothelial cells, molecules are released that attract leukocytes and platelets and adhesion molecules for these cells are also exposed in the endothelium. It has also been demonstrated that the leukocytes that adhere are primarily monocytes that release tissue factor (TF) and neutrophils that release enzymes and form neutrophil extracellular traps (NETs), which activate coagulation factors and deactivate natural anticoagulants.[12-14] Von Brühn et al.[15] have shown in a highly illustrative manner, using scanning electron microscopy, that induction of stenosis in the vena cava of mice does not provoke morphological injury to the endothelium. However, they observed that after 1 hour leukocytes began to roll along the endothelium and after 6 hours the surface of the endothelium was covered by a layer of these cells. Using intravital microscopy, they showed that these leukocytes were primarily monocytes and neutrophils. They also showed presence of NETs in thrombi and their role in formation and progression of the thrombus by activation of the intrinsic coagulation system. To achieve this, they used transgenic animals with neutropenia or with factor XII deficiency and animals in which NETs were lysed by DNase, in which formation of thrombus would not occur.

The following question therefore arises: could it be possible to use substances with anti-inflammatory activity that inhibits these mechanisms and with weaker or nonexistent systemic anticoagulant effects to treat venous thrombosis (VT)?

Based on the knowledge described above, a number of different substances have been used with the objective of inhibiting molecules responsible for attraction or adhesion of inflammatory cells, such as P-selectins and E-selectins, or of inhibiting enzymes released by these cells, which locally activate the coagulation system or act at some point in this initial sequence of events involved in thrombi development, in the hope of impeding their formation or progression, without interfering with systemic coagulation.

Many different studies published by Dr. Wakefield's University of Michigan team have demonstrated the antithrombotic activity of P-selectin inhibitors (an adhesion molecule for platelets and leukocytes), both in a model of thrombosis induced by ligature of

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the vena cava in rats[16,17] and in monkeys, inducing thrombosis in the vena cava or iliac veins using balloon occlusion.[18-21]

Culmer et al.,[22] part of the same team, using an E-selectin inhibitor for prevention and treatment of thrombosis in a model of vena cava stasis in mice, also demonstrated an inhibitory effect on formation and extension of thrombi in a similar manner to enoxaparin, in relation to a control group, without changing the bleeding time, as occurs with enoxaparin.

In a study along the same lines, we tested substances with anti-inflammatory activity for prevention of VT in the Protein Purification Laboratory, Department of Biochemistry, UNIFESP (Prof. Dr. Maria Luiza Vilela Oliva), using the recombinant inhibitor rBbCI,[23] the original protein of which has demonstrated inhibitory actions on elastase, cathepsin-G,[24] proinflammatory enzymes that are also inhibited by heparin.[25] The rBbCI inhibitor also reduced levels of interleukin-8, a cytokine that primarily stimulates migration of neutrophils to the focus of inflammation.[24] In a model of vena cava ligature in rats, rBbCI had an inhibitory effect on development of the thrombus similar to that of heparin and, like heparin, the action was dose-dependent.[26] However, rBbCI did not change activated partial thromboplastin time or bleeding time in the animals' tails, which were identical to times in control animals. The anti-inflammatory activity of heparin, responsible for inhibition of adhesion of leukocytes to the activated endothelium, in conjunction with its anticoagulant activity, had been proposed previously and may, in this model, participate in the antithrombotic effect of heparin.[27]

In clinical trials, it has been observed that statins, and particularly rosuvastatin, exert a certain protective effect against development of venous thromboembolism.[28] It has been suggested that one of the mechanisms of this effect is the anti-inflammatory role played by these medications. However, these results are considered preliminary and additional evidence is needed to justify using these drugs for this purpose.[29-31]

The results observed with these various different substances with anti-inflammatory activity in the different animal models of VT and, in the case of statins, in clinical studies, are encouraging and suggest the possibility that we are on course towards a new class of medications which, with little or no hemorrhagic effect, can be used for prophylaxis and treatment of venous thromboses with greater safety. These results also suggest that the prophylactic effect of anticoagulants used at doses lower than those for treatment of VT may be, at least in part, because of a local anti-inflammatory effect.

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Perspectivas futuras na abordagem profilática e terapêutica da trombose venosa: substâncias antitrombóticas com menor risco hemorrágico?

Future prospects for prophylactic and therapeutic management of venous thrombosis: antithrombotic substances with lower risk of hemorrhage?

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Os anticoagulantes são medicamentos essenciais no tratamento e na profilaxia do tromboembolismo venoso desde a década de 40 do século passado, com a utilização da heparina e das anti-vitaminas K. Porém, mesmo com a introdução das heparinas de baixo peso molecular, do fondaparinux e, mais recentemente, dos anticoagulantes orais diretos, existe ainda um risco não desprezível de hemorragias significativas e mesmo letais[1-4].

Os conhecimentos adquiridos nas últimas décadas, principalmente a partir de estudos experimentais, sugerem que o sistema imunológico e as células inflamatórias têm papel na ativação inicial e localizada da coagulação nas veias que desencadeia a trombose, principalmente nas situações em que existe diminuição ou bloqueio do fluxo sanguíneo[5-8]. Essa situação de estase ocorre no ser humano em casos de compressão venosa e de repouso no leito por doença clínica ou cirurgia, e também durante anestesia, imobilização por trauma, paralisia e viagens prolongadas[9-11].

Estudos em modelos experimentais de trombose provocada pela diminuição ou parada de fluxo sanguíneo induzidas por estenose ou ligadura em veia cava de roedores, sugerem que, em decorrência da isquemia e da ativação das células endoteliais, haveria liberação de moléculas que atraem leucócitos e plaquetas e também exposição de moléculas de adesão dessas células ao endotélio. Foi demonstrado também que os leucócitos aderidos são principalmente monócitos que liberam fator tecidual (FT) e neutrófilos que liberam enzimas e formam as armadilhas extracelulares de neutrófilos (*neutrophil extracellular traps*, NETs), que ativam fatores de coagulação e inativam anticoagulantes naturais[12-14]. Von Brühn et al.[15] mostraram, de maneira muito ilustrativa, por microscopia eletrônica de varredura, que a realização de estenose na veia cava de camundongos não provoca lesão morfológica do endotélio. Porém, os autores observaram que, após 1 hora, se iniciava o rolamento de leucócitos sobre o endotélio, e que, após 6 horas, a superfície endotelial estava coberta por uma camada dessas células. Mostraram também, por microscopia intravital, que os leucócitos eram principalmente monócitos e neutrófilos. Mostraram, ainda nos trombos, a presença de NETs e seu papel na formação e na progressão do trombo pela ativação do sistema intrínseco da coagulação. Para tal, utilizaram animais transgênicos com neutropenia ou com deficiência de fator XII e animais em que as NETs foram lizadas por DNase, nos quais não havia formação do trombo.

Surge então a pergunta: seria possível utilizar, na terapia da trombose venosa (TV), substâncias com ação anti-inflamatória que inibissem esses mecanismos e com menor ou nenhuma ação anticoagulante sistêmica?

Baseados nos conhecimentos acima referidos, foram utilizadas diferentes substâncias com a finalidade de inibir moléculas de atração ou adesão de células inflamatórias, como as P e as E-selectinas, ou inibir enzimas liberadas por essas células, que ativam localmente o sistema de coagulação ou agem em algum ponto dessa sequência de eventos iniciais no desenvolvimento de trombos, visando impedir sua formação ou progressão, sem interferir na coagulação sistêmica.

Inúmeros trabalhos do grupo do Dr. Wakefield, da Universidade de Michigan, mostraram a ação antitrombótica de inibidores da P-selectina, molécula de adesão de plaquetas e leucócitos, tanto em modelo de trombose induzida por ligadura de veia cava de ratos[16,17] como em macacos, induzindo a trombose na veia cava ou em veias ilíacas, por meio de balão oclusor[18-21].

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Culmer et al.[22], do mesmo grupo, utilizando um inibidor da E-selectina para prevenção e tratamento de trombose em modelo de estase na veia cava de camundongos, também mostraram efeito inibidor da formação e extensão de trombos de maneira similar à enoxaparina, em relação ao grupo controle, sem alteração do tempo de sangramento (TS), como ocorreu com a enoxaparina.

Em um trabalho nessa linha testando substâncias com ação anti-inflamatória na prevenção da TV, realizado no Laboratório de Purificação de Proteínas do Departamento de Bioquímica da UNIFESP (Profa. Dra. Maria Luiza Vilela Oliva), utilizamos o inibidor recombinante rBbCI[23], cuja proteína original demonstrou ter ação inibidora de elastase, de catepsina-G[24], enzimas pró-inflamatórias também inibidas pela heparina[25]. Além disso, o rBbCI reduziu os níveis de interleucina-8, citocina que estimula principalmente a migração de neutrófilos para o foco inflamatório[24]. No modelo de ligadura da veia cava em ratos, o rBbCI teve ação inibitória do desenvolvimento do trombo similar à da heparina, e como ela, teve ação dose dependente[26]. O rBbCI não alterou o tempo de tromboplastina parcial ativada nem o TS na cauda dos animais, que foram iguais aos dos animais controle. A ação anti-inflamatória da heparina, responsável pela inibição da adesão de leucócitos ao endotélio ativado juntamente com sua ação anticoagulante, já havia sido levantada anteriormente, podendo, nesse modelo, ter participação no efeito antitrombótico da heparina[27].

Em ensaios clínicos, foi verificado que as estatinas, principalmente a rosuvastatina, exercem um certo efeito protetor contra o desenvolvimento do tromboembolismo venoso[28], sendo sugerido como um dos mecanismos dessa ação o papel anti-inflamatório desses medicamentos. Entretanto, são resultados considerados preliminares, necessitando novas evidências para justificar a utilização de tais medicamentos com essa indicação[29-31].

Os resultados verificados com essas várias substâncias com ação anti-inflamatória em diferentes modelos animais de TV e, no caso das estatinas, em estudos clínicos, são animadores e sugerem a possibilidade de estarmos no caminho de uma nova classe de medicamentos que, com pouco ou nenhum efeito hemorrágico, possam ser utilizados com mais segurança na profilaxia e no tratamento das tromboses venosas. Esses resultados sugerem também que o efeito profilático de anticoagulantes usados em doses menores do que as de tratamento da TV possa ser, pelo menos em parte, devido a uma ação anti-inflamatória local.

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