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Influence of Various Types of Hormonal Agents Used from the Position of Contraception on the Dynamics of the Functional State of the Endothelium and Varicose Transformation of the Pelvic Veins

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Abstract It was found that the development of DE in VRVMT is characterized by an increase in the number of CEC and the level of biochemical markers (VCAM-1, P-and E-selectins). An increase in the level of CEC over 5, 7x104 / l cells, VCAM-1-300 ng / ml, P-selectin -170 ng / ml and E-selectin-50 ng / ml confirms the development of ED.

Keywords Uterus, Varicose veins, Pelvis, Contraception, Estrogen, Progesterone, Endothelium, Combined oral tablets

1. Introduction

Considering the pathogenesis of varicose veins of the small pelvis, it is necessary to immediately note their versatility and sufficient complexity. Before analyzing the pathogenesis of varicose veins, it is necessary to consider some aspects of the normal physiology of the venous wall and, above all, its endothelium, which have been determined only recently. Endothelial cells secrete two unstable vasodilators: prostacyclin (prostoglandin I2) and nitric oxide NO (i.e. nitric oxide), as well as a highly physiologically active peptide, the vasoconstrictor endothelin-1. Prostacyclin and nitric oxide act as oral hormones with many common features [1,3,5,8,9,13]. Prostaglandin I2 (prostacyclin) is a powerful inhibitor of platelet aggregation and less powerful in suppressing their adhesion to the endothelium. It also reduces vascular tissue proliferation (by reducing mitogen synthesis), with little or no effect on vascular tone. Nitric oxide is a powerful vasodilator and a stronger inhibitor of platelet adhesion to the endothelium than prostacyclin, having little effect on their aggregation. Nitric oxide inhibits endothelial proliferation. In endothelial cell culture, the production of prostacyclin and nitric oxide increases simultaneously, through intermediaries such as bradykinin, ADP (adenosine diphosphate), and thrombin. Thus, the basal production of vasodilators by the endothelium is under constant control of blood flow.

Growth factors — polypeptide chemical agents produced in situ by vessel wall cells (endothelial, smooth muscle cells) and blood cells (platelets, leukocytes) play a crucial role in pathological changes in the pelvic venous system [4,6,7,10,11,12].

Based on the analysis of literature data, the following indicators can potentially be considered as markers of venous dilation and venous stasis, cell damage and pathological venous rearrangement: vasoactive substances: endothelin-1, prostacyclin; adhesion molecules (ICAM-1, VCAM-1, ELAM-1, etc.); substances of the selectin group: E -, p -, and L-selectin; growth factors: TGF, FGF, VEGF; circulating endothelial cells; inflammatory mediators: PAF, tumor necrosis factor, interleukins 1 and 6, thromboxane A2, etc.

Given the key role of endothelial dysfunction in the pathogenesis of varicose veins, our choice was made in favor of determining the diagnostic significance of determining the degree of endothelial damage in peripheral vein diseases when using oral contraceptives in women of reproductive age. Among the markers of endothelial dysfunction in venous diseases, such indicators as the above-described endothelin-1, adhesion molecules, etc. are considered. The short lifetime of these substances is unlikely to help us judge reliable and long term damage to the endothelium venous system of the small pelvis and lower extremities.

According to the literature and our practical experience, taking hormonal drugs is associated with the risk of developing venous thromboembolic complications (VTE) – deep vein thrombosis (DVT), pulmonary embolism (PE), which can be fatal (1-2% of VTE cases). Soon after, reports of the first cases of venous thrombosis associated with the use of an oral contraceptive began to appear. The use of

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estrogens in oral contraceptives and hormone replacement therapy leads to many changes in the coagulation system. Further studies have shown that the effect of progestogen, which is part of the COC, is also related to increasing the risk of VTEO. In the 1970s and 1980s, the second and third generations of Progestogens appeared. It has been shown that users of third-generation COC have a higher risk of venous thrombosis than those using second-generation COC. thus, taking hormonal drugs is associated with an increased risk of VTE. These risks differ depending on the composition of the drug (the dose of estrogen, the type of progestins) and how they are used.

2. Materials and Methods

The study of the effect of various types of hormonal agents used in contraception on the dynamics of the functional state of the endothelium was conducted in 92 patients with VRVMT.

3. The Results of Research

These patients formed a group of patients with the presence of HRVMT and received estrogens and gestagens for the purpose of contraception. Depending on the type of funds used, the patients were divided into two subgroups. Subgroup 1 (n=50) included patients who used estrogens, and subgroup 2 (n=42) included patients who used Progestogens. The number of healthy women was 30 (control group). Comparative characteristics of the biochemical parameters of ED, before the use of contraception.

The analysis of the obtained results revealed the initial close to the control values of the CEC level to 5.02±1.8 cells x104/l (M±m) and 4.3±0.5 cells x104/l (M±m) in two subgroups, respectively. After using contraceptives in 3 months, this indicator increased to 7.89±2.7 cells x104/l (M±t) in subgroup 1 and 7.2±2.1 cells x104/l (M±t) in subgroup 2 ($p>0.05$). After 6 months of contraceptive use, this indicator increased to 10.8±4.3 x104 cells/l (M±t) in subgroup 1 and 9.6±3.2 x104 cells/l (M±t) in subgroup 2 ($p>0.05$). There are no significant differences between the subgroups. The increase in CEC after the use of hormonal agents is obviously associated with damage to the integrity of the endothelial cell layer, which extends to other veins.

After 6 months of contraception, the number of CEC practically corresponded to the norm, there was an increase in this indicator to 10.8±4.3 x104 cells/l in group 1 and 9.6±3.2 x104 cells/l (M±m) ($p<0.05$) in subgroup 2.

The level of endothelemia according to the CEC number was slightly higher after using contraceptives containing estrogens ($p>0.05$), which can be explained by the greater effect on the endothelium when using estrogens, exfoliation of ECS and their further free circulation in the bloodstream. a Similar pattern was observed in both groups with VCAM-1 concentrations. With an initially elevated level of 299.6±83.8 ng / ml (M±t) in subgroup 1 and 251.8±86.9 ng/ml (M±t) in subgroup 2, a pronounced spike in VCAM-1 concentration was detected after 2 months of contraceptive use. In the 1st subgroup up to 367.2±76.2 ng / ml (M±t) and in the second subgroup - up to 357.6±66.3 ng/ml (M±t). The inflammatory response was more pronounced 6 months after the use of contraceptives, as evidenced by statistically significant lower VCAM-1 indicators. The increased concentration of this marker after contraception also indicates increased adhesion of white blood cells to EC and is a reflection of the effect of estrogens and progestins on the vascular endothelium due to changes. 6 months after the use of contraceptives, including the use of estrogens and progestins, the VCAM-1 indicators in 2 subgroups significantly increased, approaching the values of 460.9±74 ng / ml (M±t) and 477.7±77.4 ng/ml (M±t), respectively ($p<0.05$). It should be noted that the concentration of VCAM-1 in patients after progestin use (subgroup 2) was significantly higher (477.7±77.4 ng/ml (M±t)), which once again confirms a more effective negative effect on the function of the endothelium of progestins. The concentrations of P - and E - selectins before the use of contraceptives were initially close to those of the control group ($p<0.05$). After the course of contraceptive use, there was a tendency to increase these indicators. There were no statistically significant differences between the groups. After 6 months of therapy, there was an increase in P-selectin to values of 191.9±35.7 and an increase in the concentration of E-selectin 48.5±10.8. The appearance of P-and E-selectins on the surface of the endothelium occurs very quickly, and also increases as a result of the influence of estrogens and Progestogens. Having provided the initial stage of the cascade of inflammatory reactions in the endothelium of the veins, both in the case of varicose veins of the small pelvis, and in response to the use of hormonal agents, their number increases and phase 2 of persistent adhesion of white blood cells begins, which occurs after 2 months of using contraception. The obtained results indicate significant changes in the endothelial cells of the vascular bed and a violation of flebodynamic , when using hormonal methods.

The difference in the concentrations of endothelin-1 and tissue plasminogen (t - PA) before and after the use of hormonal contraceptives was not significant ($p>0.05$). However, their concentrations at the initial determination in both subgroups were underestimated in comparison with the control group. This indicates a reduced functional activity of the endothelium, inhibition of the activity of the coagulation system.

Of course, many aspects of the pathogenesis of varicose veins remain completely unclear. The study was only a small step towards understanding the problem. Answers to many questions, as well as subsequent studies devoted to identifying the most significant causes of pathological processes of the venous wall that precede the appearance of its irreversible changes, will undoubtedly contribute to improving the system of prevention of venous diseases and improving the quality of treatment of patients with VRVMT.

In this work, we have convincingly shown the role of the inflammatory element in the occurrence of disorders in the functioning of the venous endothelium on clinical and laboratory material. The hypothesis of the existence of a "leukocyte trap" at the level of varicose veins was confirmed, "breakdown" in the endothelial lining system at the local level was clearly demonstrated at the clinical and laboratory level, and VCAM-1 expression proved endothelial activation in patients with VRVMT when using two types of hormonal agents (estrogens and gestagens) for oral contraception.

It was found that the development of DE in VRVMT is characterized by an increase in the number of CEC and the level of biochemical markers (VCAM-1, P-and E-selectins). An increase in the level of CEC over 5, 7x104 / l cells, VCAM-1-300 ng / ml, P-selectin -170 ng / ml and E-selectin-50 ng / ml confirms the development of ED.

The cytomorphological picture of the endothelium in VRVMT in comparison with the unaffected venous wall is characterized by polymorphism and heterogeneity in combination with specific cell reorganization. This is confirmed by a statistically significant increase in the frequency of detection of giant ECS (up to 14±5%), as well as desquamated ECS (up to 15±2%).

The character used contraception at VRWM affects the dynamics of markers of ED. A higher injury rate in group I patients who used estrogens compared to group II patients was accompanied by a statistically significant increase in the level of CEC and VCAM-1 and a decrease in the concentration of P - and E-selectins starting from 2 months of use and immediately after 6 months.

It can be noted that in patients with VRVMT, it is possible to use these markers as an additional diagnostic criterion in assessing the functional state of the endothelium, during the period of contraception, and timely correct developing changes in the venous system of the small pelvis and lower extremity, in order to prevent thrombembolic complications.

It is clearly not possible to consider the described mechanisms as an alternative. It is logical to assume the interaction of both the hormonal factor and hemodynamic changes. Without disputing their role in the occurrence of VRVMT, it should be noted that this idea of the mechanisms of the disease development is consistent with modern ideas about the etiopathogenesis of varicose veins of the small pelvis and lower extremities. Therefore, it is logical to assume that the pathological process is also based on the mechanisms of violation of leukocyte-endothelial interaction, inflammation of the venous wall and its remodeling.

Undoubtedly, this issue needed further in-depth study.

In summary, we can note that the analysis of the dynamics of ED markers (CEC, VCAM-1, P-selectin, E-selectin, t-PA, endothelin-1) in different periods of use of estrogens and gestagens in patients with VRVMT indicates the degree of severity of ED and can serve as an estimated marker of the activity of varicose vein transformation processes in the chronic course of the disease. This makes it possible to timely carry out therapeutic corrective measures using phlebotropic drugs that have a polyvalent effect and predict the progression of HRVMT.

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