



Research Article

Prognosis of Venous Thromboembolic Complications after Hip Replacement on the Background of Modern Thromboprophylaxis

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Abstract

The objective of the study is to determine sufficient Thrombogenic Risk (TR) factors of post-operative Venous Thromboembolic Complications (VTEC) development on the background of modern thromboprophylaxis including non-pharmacological and pharmacological implications.

Materials and methods

The observation data of 351 patients who underwent primary total Hip Replacement (HR) are presented in the article. The interview of patients and the study of medical documentation were carried out. Some laboratory (as well as genetic) analysis methods were used to reveal the potential TR factors.

Results

Six TR factors out of 26 were determined to increase the possibility of VTEC occurrence significantly. They are type 2 diabetes mellitus (odd ratio OR 5.6; 95% confidence interval CI 1.8-17.0), female sex (OR 4.6; CI 1.5-13.6), low level of physical activity (OR 4.4; CI 1.7-11.1), age over 60 (OR 4.3; CI 1.8-10.6), increased level of D-dimers before operation (OR 3.5; CI 1.4-8.9) and varicose disease of the lower extremities (OR 3.4; CI 1.5-7.7).

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Citation: Momot AP, Berezhnyak IV, Merkulov IV, Zateev AV (2017) Prognosis of Venous Thromboembolic Complications after Hip Replacement on the Background of Modern Thromboprophylaxis. J Hematol Blood Transfus Disord 4: 013.

Received: December 01, 2016; **Accepted:** January 27, 2017; **Published:** February 13, 2017

Conclusion

Revealed TR factors allow for determining the group at high risk of VTEC after HR and developing approaches to the individual thromboprophylaxis among these patients.

Keywords: Anticoagulant prophylaxis; Hip replacement; Prognosis; Thrombogenic risk factors; Venous thromboembolic complications

Abbreviations

CAD - Coronary Artery Disease

DM - Diabetes Mellitus

DVT - Deep Vein Thrombosis

HR - Hip Replacement

MTHFR - Methylene tetrahydrofolate Reductase

SFMC - Soluble Fibrin-Monomeric Complexes

TR - Thrombogenic Risk

VDLE - Varicose Disease of the Lower Extremities

VTEC - Venous Thromboembolic Complications

Introduction

According to the modern concepts, venous thrombosis and thromboembolic syndrome belong to the most common and socially significant diseases. The frequency of some new symptomatic cases of VTEC only in the USA and Europe reaches more than 1.6 million annually, accounting for about 10% of all deaths in hospital [1]. The described vascular events are often the cause of disability and mortality in patients undergoing HR [2,3]. Therefore, in the absence of the effective thromboprophylaxis, the frequency of Deep Vein Thrombosis (DVT) after total HR reaches 57%, fatal pulmonary embolism ranges from 0.1 to 2%, and severe post-thrombotic syndrome develops in 5-10% of patients with DVT [3].

The practical application of modern schemes of pharmacological and non-pharmacological prevention of venous thromboembolism has improved the results of surgical treatment in orthopedic patients [4]. The use of some modern oral anticoagulants for VTEC prevention in this category of patients becomes more popular [5]. Nevertheless, the problem of venous thromboembolism in total HR is still relevant [5].

To reduce thrombotic complications on the background of the regulated pharmacoprophylaxis, registration, and modification of individual TR factors can be important, as evidenced by a number of authors [6]. However, it should be considered that currently more than 100 of such factors have been described, which can individually or in combination lead to vascular catastrophes [4,6].

The continuation of the studies of the occurrence and the role of certain thrombogenic risk factors in each specific case and the possibility of their management can be a significant contribution towards further reduction of the number of postoperative VTEC. In the light of the above, the aim of this work was to identify the significant TR factors after primary unilateral total HR in patients receiving modern anticoagulants - enoxaparin, rivaroxaban or dabigatran etexilate.

Material and Methods

In the period from 2010 to 2013, a prospective randomized study was conducted based on the department of orthopedics and anesthesiology and the department of reanimation of the Regional clinical hospital in Barnaul. The Committee on Biomedical Ethics approved the work.

The study included 351 patients: 156 men (44.4%) and 195 women (55.6%). The inclusion and exclusion criteria were the same as in the studies RECORD 2 and RE-NOVATE [2,7]. In particular, inclusion criteria included: patients ≥ 18 years and >40 kg, scheduled for primary elective unilateral total hip replacement who provided signed informed consent, were eligible for study. Exclusion criteria included: any bleeding diathesis; history of acute intracranial disease or hemorrhagic stroke; major surgery, trauma, uncontrolled hypertension or myocardial infarction within the past 3 months; gastrointestinal or urogenital bleeding or ulcer disease within the past 6 months; severe liver disease; aspartate aminotransferase or Alanine Aminotransferase (ALT) levels more than two times the Upper Limit of the Normal Range (ULN) within the past month; severe renal insufficiency (creatinine clearance <30 mL min⁻¹); concomitant long-acting non-steroidal anti-inflammatory drug therapy (also contraindicated during study treatment); active malignant disease; and pregnancy. All patients were hospitalized with coxarthrosis of 2-3 degrees and after randomization were divided into three groups depending on the anticoagulant used - enoxaparin (156 patients), dabigatran etexilate (122 patients), and rivaroxaban (73 patients).

The patients received the first dose of direct oral anticoagulants immediately after surgery. In the case of rivaroxaban, the patients were given 10 mg of the agent 8 hours after surgery (subsequently once daily at the same dose for 30 days). If dabigatran etexilate was prescribed, the agent was given at a dose of 110 mg within 4 hours after surgery (then 220 mg daily for 30 days). Enoxaparin was used 12 h before surgery (in a dose of 40 mg), re-administered 12 h after surgery (at the same dose), and subsequently once daily for 10 days (at the same dose). This regimen of enoxaparin sodium was prescribed by the local protocol. In the postoperative period, the pharmacoprophylaxis of all patients was combined with elastic compression of the lower extremities and early activation [2,4,5]. Fibrinolysis inhibitors for the prevention of hemorrhagic complications were not used. DVT was diagnosed on the basis of known clinical and instrumental data [2,4]. To visualize thrombosis, ultrasound angioscanning of lower extremities was used - before surgery, on the 3rd, 5th, 10th day, and also after 1 and 3 months.

To identify potential TR factors in the preoperative period, a survey of patients and a study of medical records were carried out, and some laboratory, as well as genetic, analysis methods were used. For this purpose, before the operation, evaluation of psycho-emotional stress was performed as well as athletic ability assessment of the patients with Rivermead index, which could range from 0 (inability to self-perform any voluntary movements) to 15 points (able to run 10 m) [8]. Psychological status was assessed using a psychometric test adapted for Russia - "hospital scale of anxiety and depression HADS (Hospital Anxiety and Depression Scale).

According to the recommendations, the smokers were considered to be individuals who smoked more than one cigarette per day. Obesity was diagnosed when body mass index was $\geq 30,0$ kg/m², arterial hypertension when systolic blood pressure increased over 140 mmHg or diastolic blood pressure increased above 90 mmHg, Coronary Artery

Disease (CAD), varicose diseases of the lower extremities, are clinical manifestations according to the CEAP classification from C2 to C4 [9], type 2 Diabetes Mellitus (DM) and impaired glucose tolerance.

In the analysis of the laboratory methods, the data of common blood test, platelet aggregation with adenosine diphosphate, fibrinogen concentration (according to Clauss), the amount of Soluble Fibrin-Monomeric Complexes (SFMC), D-dimer levels using a test system, factor XIII activity, C-reactive protein concentration, homocysteine levels in serum were taken into account. These studies were carried out in accordance with the instructions for the reagent sets and based on existing recommendations. In addition, carriage of number of prothrombotic mutations and polymorphisms of protein genes involved in hemostasis reactions - FII (genotype G20210 G/A), prothrombin factor; factor V Leiden (genotype 1691 G/A); PAI-1 (genotypes 675 5G/4G and 675 5G/4G) - plasminogen activator inhibitor and methylenetetrahydrofolate reductase - MTHFR (genotypes 677 C/T and 677 T/T) were established in the patients.

Statistical analysis was performed using Microsoft Office Excel 2003, Statistica 6.1 software (StatSoft Inc.) and an application program SAS JMP 9.2 Software for Windows. To perform statistical processing of the data, calculations were made using the statistical tools: χ^2 (chi-square), the bilateral Fisher test, and Yates correction depending on the calculated frequency for contingency tables 2x2. Results were considered to be statistically significant when $p < 0.05$. Probabilistic assessment of risk factors was performed by univariate analysis calculating Odds Ratios (ORs) and 95% CIs. Multivariate analysis was performed by binary logistic regression method. The regression model included variables with a significance value of $p < 0.05$, obtained by univariate analysis.

Results

The age of patients ranged from 30 to 74 years (mean age of 57.3 ± 9.7 years), body weight - from 54 to 158 kg (mean weight of 81.1 ± 15.3 kg).

To search for significant TR factors, which determine the possibility of the development of VTEC after total HR, the data of patients with venous thrombotic complications were used. There were 25 such cases or 7.1% of the total number of the observed patients including one patient (0.3%) receiving thromboprophylaxis using enoxaparin sodium, who was diagnosed nonmassive pulmonary embolism on the second day after surgery. It was determined that VTECs occurred more often (2.6 times) in the period up to 5 days after surgery ($n=18$; 5.1%) in comparison with the period from 10 to 30 days ($n=7$; 1.9%; $p < 0.05$). It should be noted that three months after surgery, no cases of venous thrombosis were registered, and in 16 patients (64%) VTECs were clinically asymptomatic.

It is notable that in the present work, despite the increase in the number of thrombosis by 1.9-2.5 times in patients receiving enoxaparin, no statistically significant differences were detected between the groups of patients receiving different anticoagulants that corresponded to previously published data [1] (Table 1).

In this regard, in further calculations, the role of various TR factors was taken into account regardless of the anticoagulant type. Association of known and considered TR factors with venous thrombosis and their prognostic significance are presented in table 2 and table 3.

| Anticoagulant | Number of Patients | VTEC, n(%) | Verification Time of VTEC After Surgery | |
|----------------------|--------------------|------------|---|-------------|
| | | | Upto 5 Days | 5 - 30 Days |
| Enoxaparin | 156 | 16(10,3%) | 11(7,1%) | 5(3,2%) |
| Dabigatran etexilate | 122 | 5(4,1%) | 4(3,3%) | 1(0,8%) |
| Rivaroxaban | 73 | 4(5,5%) | 3(4,1%) | 1(1,4%) |
| Total | 351 | 25(7,1%) | 18(5,1%) | 7(1,9%) |

Table 1: The analysis of VTEC in patients after HR depending on the anticoagulant and detection time.

| Thrombogenic risk factor | Patients (n=351), % | | OR(95% CI) | p |
|---|---------------------|-----------------|----------------|----------|
| | Without DVT (n=326) | With DVT (n=25) | | |
| Type 2 diabetes mellitus | 4.3 | 20.0 | 5.58(1.8-17.0) | 0.004** |
| Female sex | 53.4 | 84 | 4.58(1.5-13.6) | 0.003*** |
| Low level of physical activity (according to Rivermead index <14 point) | 40.8 | 75.0 | 4.35(1.7-11.1) | 0.001** |
| Age of 60 years and over | 37.4 | 72.0 | 4.30(1.8-10.6) | 0.001** |
| Impaired glucose tolerance | 3.1 | 12 | 4.31(1.1-16.8) | 0.057 |
| D-dimer level >500 ng/ml | 10.1 | 28.0 | 3.46(1.4-8.9) | 0.017** |
| Varicose disease of the lower extremities | 19.0 | 44.0 | 3.35(1.5-7.7) | 0.003 |
| Thrombosis in personal anamnesis | 7.4 | 16.0 | 2.40(0.8-7.6) | 0.17 |
| Coronary artery disease | 7.4 | 16.0 | 2.40(0.8-7.6) | 0.17 |
| Factor V Leiden mutation (genotype 1691 G/A) | 3.7 | 8.0 | 2.28(0.2-8.7) | 0.28 |
| Hyperfibrinogenemia (>5.0 g/l) | 12.3 | 24.0 | 2.26(0.9-6.0) | 0.27 |
| Factor XIII activity (>140 %) | 40.8 | 60.0 | 2.18(1.0-5.0) | 0.26 |
| Anxiety/depression level (≥11 points) | 22.4 | 37.5 | 2.07(0.9-4.9) | 0.37 |
| Hyperhomocysteinemia (>15 μmol/l) | 39.3 | 56.0 | 1.97(0.9-4.5) | 0.39 |
| C-reactive protein level >5.0 mg/ml | 10.1 | 17.6 | 1.89(0.6-5.6) | 0.79 |
| Obesity (BMI ≥30) | 37.7 | 48.0 | 1.52(0.7-3.5) | 0.81 |
| Arterial hypertension | 17.5 | 24.0 | 1.49(0.6-3.9) | 0.93 |
| Polymorphism of the MTHFR gene (genotypes 677 C/T and 677 T/T) | 18.1 | 24.0 | 1.43(0.6-3.8) | 0.95 |
| Polyglobulia* | 35.3 | 40.0 | 1.22(0.5-2.8) | 0.99 |
| Hyperaggregation of platelets (>80%) | 17.5 | 20.0 | 1.18(0.4-3.3) | 1.00 |
| Blood group is not "0" | 63.5 | 64.0 | 1.02(0.4-2.4) | 1.00 |
| Leukocytosis (>8,0 × 10 ⁹ /l) | 18.1 | 16.0 | 0.86(0.3-2.6) | 1.00 |
| Polymorphism of PAI-1 gene (genotype 675 5G/4G and 675 5G/4G) | 44.8 | 36.0 | 0.69(0.3-1.6) | 0.89 |
| Increased level SFMC (>10 mg/100 ml) | 22.4 | 16.0 | 0.66(0.2-2.0) | 0.95 |
| Active smoking | 19.0 | 12.0 | 0.58(0.2-2.0) | 0.91 |
| Prothrombin mutation (genotype G20210 G/A) | 1.2 | 0 | – | – |

Table 2: Univariate analysis of the prognostic significance of various TR factors in patients after total hip replacement.

| Combination of TR factors | All patients (n=351), % | | | Patients over 60 years (n=140), % | | |
|-----------------------------|-------------------------|----------------|------------------|-----------------------------------|-----------------|------------------|
| | Without DVT (n=326) | With DVT (=25) | OR(95% CI) | Without DVT (n=122) | With DVT (n=18) | OR (95%CI) |
| Hyperglycemia*, AH, obesity | 2.2 | 16.0 | 8.5(2.3-31.8)** | 0 | 16.7 | – |
| AH, obesity | 11.0 | 40.0 | 5.4(2.3-12.9)*** | 12.1 | 44.4 | 5.8(2.0-17.0)*** |
| Hypodynamia, obesity | 16.2 | 44.0 | 4.1(1.8-9.4)*** | 14.9 | 55.6 | 7.2(2.5-20.5)** |

Table 3: Univariate analysis of the prognostic significance of combination of thrombogenic risk factors for VTEC development after the initial HR.

Note: * - Hemoglobin >160 g/l and the number of red blood cells >5,0 × 10¹²/l in men, Hemoglobin >140 g/l and the number of red blood cells >4,5 × 10¹²/l in women; ** -χ² with Yates correction; *** - Fisher's exact test (bilateral).

Given that not all the TR factors in the study demonstrated their significance in the analysis in isolation from one another, we divided a number of studied factors into clusters based on age (<60 years and ≥60 years). The basis for this stratification of TR factors was their

frequent association in patients in our study. The results of univariate analysis of clusters data are shown in table 3.

A multivariate analysis was also carried out taking into account the TR factors, the significance of which has been demonstrated above. The obtained data are presented in table 4.

| Thrombogenic Risk Factor | Estimate | Standard Error | Wald Chi-Square | Pr>ChiSq | OR (Standardized Estimate) | P |
|------------------------------|----------|----------------|-----------------|----------|----------------------------|--------|
| Thrombosis probability | -0,0429 | 0,0223 | - | - | - | - |
| Type 2 DM | 0,1570 | 0,0587 | 5,3568 | 0,0206 | 4,7902 | 0,0286 |
| Rivermead mobility index <14 | 0,07210 | 0,0267 | 6,8079 | 0,0091 | 7,7509 | 0,0054 |
| Age≥60 лет | 0,0598 | 0,0281 | 2,9818 | 0,0842 | 3,1404 | 0,0764 |
| Female sex | 0,0565 | 0,0281 | 5,1136 | 0,0237 | 6,0470 | 0,0139 |
| D-dimers >500 ng/ml | 0,0913 | 0,0433 | 3,8949 | 0,0484 | 3,6482 | 0,0561 |
| VDLE | 0,0620 | 0,0329 | 2,9509 | 0,0858 | 2,8490 | 0,0914 |

Table 4: Multivariate analysis of prognostic significance of TR factors in patients after total hip replacement.

Note: * - Type 2 DM or impaired glucosetolerance; AH - Arterial Hypertension; Difference from the value of the corresponding index of patients without DVT was statistically significant at p<0.005 (**), p<0.001 (***).

Discussion

In the present study some studied metabolic disorders like type 2 DM, gender differences, reduced mobility in the preoperative period, age over 60 and increased levels of D-dimers in blood plasma prior to surgery and Varicose Disease of the Lower Extremities (VDLE) were included in a number of important TR factors, which significantly (on average 3.35-5.58 times; 95% CI) increase the risk of VTEC development [4].

In particular, according to our data, patients suffering from type 2 DM, the presence of which increased the probability of VTEC occurrence (according to OR) by 5.58 times (Table 2), had the greatest risk of VTEC. This fact can be associated with naturally occurring endothelial dysfunction of blood vessels with this type of metabolic disorders on the background of the action of pro-inflammatory cytokines with the acquisition of prothrombogenic properties. However, there are some studies in this field, according to which the effect of this TR factor on the risk of VTEC in orthopedic surgery remains unclear [10-13].

The second most important TR factor was gender differences. Female patients were associated with the increase of thrombotic complications by 4.58 times. This pattern was described in the studies of many other authors, who took into account the results obtained in total hip replacement and total knee replacement [11-17], although Keeney JA et al., did not find the association between the risk of thrombosis in orthopedic patients and gender differences [18].

Hypodynamia was also included to a number of significant TR factors (Rivermead mobility index <14 point) in preoperative period, that was not described earlier. This factor can lead, as it is known, to slow venous blood flow and stasis, which is an important element of the pathogenesis of venous thrombosis. For this reason, VDLE was considered as one of the most important TR factors in the study. It is associated with a lesion of the valvular apparatus of veins. As it is known, the increase of hydrostatic pressure and hypoxia in varicose veins triggers the pathological circle of venous wall reconstruction and thrombosis. Nevertheless, this association in orthopedic surgery has been recognized as controversial, especially in knee arthroplasty [10,17,19].

Another important TR factor in our study was the age over 60 years, which corresponds to the data of six previously published studies [11,14,16-18,20]. In our studies this risk factor increased the probability of VTEC occurrence by 4.3 times.

Finally, the number of informative factors that contribute to the formation of thrombosis after surgery (it was not described earlier in

large joints replacement) included an increased (more than 500 ng/ml) level of D-dimers detected at the stage of preparation of patients for surgical intervention. As it is known, this laboratory marker reflects the activation processes of blood coagulation, fibrin formation, and subsequent thrombolysis; in other words, the elevated level of D-dimers is an evidence of the thrombotic state of readiness [21]. It is quite clear that the shift of hemostatic balance towards fibrin formation before surgery can be a precondition for excessive fibrin formation after massive iatrogenic injury.

Such TR factors considered in the individual context such as thrombotic history, coronary artery disease, arterial hypertension, polyglobulia associated with increased blood viscosity, manifestation of inflammatory reaction (leukocytosis, hyperfibrinogenemia, increased levels of C-reactive protein), carriage of prothrombogenic mutations and polymorphisms, and several others did not show prognostic significance. However, the analysis of the combination of some TR factors showed the following interesting data (Table 3).

This poses the question - why did we perform an analysis of a combination of some specific risk factors? Scientific publications of recent years rightly draw attention to the fact that comorbidity may have more influence on the risk of VTEC occurrence. In particular, in view of this a number of authors used the Charlson index as a TR factor [12,15,20].

During stratification of studied TR factors we took into account the most common potentially combined pathological conditions that in elderly patients may have more frequent occurrence and severity. Thus, obesity is considered as one of the leading risk factors for developing type 2 diabetes, hypodynamia can be one of the causes of obesity and an increase in BMI is often associated with changes in hemodynamics and the development of coronary heart disease [22]. Taking into consideration the above, we have assumed that the combination of these diseases and pathological conditions may be important for determining the risk of VTEC.

In particular (Table 3), it was found that the combination of obesity, arterial hypertension and hyperglycemia contributes to the increase of the probability of VTEC occurrence in the early postoperative period by 8.5 times. It should also be noted that elderly patients with DVT had the combination of these TR factors in all cases. In addition, it is determined that low physical activity, which is a feature of patients with lesion of locomotor apparatus (coxarthrosis), in combination with obesity also significantly increased the chances of VTEC development by 4.1-7.2 times; it was influenced by the patients' age.

Subsequently, data of multivariate analysis allowed making an amendment to the dependence of TR factors (Table 4). Among the

most significant independent factors there were: hypodynamia (according to Rivermead mobility index <14 point) - OR 7.75 (p=0.029), diabetes type 2 - OR 4.79 (p=0.005), as well as female sex - OR 6.05 (p=0.014). The significance of such TR factors as age ≤60 years - OR 3.14, D-dimers level >500 ng/ml (before surgery) - OR 3.65, as well as VDLE - OR 2.85 was not confirmed in multivariate analysis (p>0.05). Nevertheless, given that the logistic regression method is sensitive to the number of analyzed variables the probability of these TR factors to be significant with more patients is very high.

To illustrate the above, we give an example of the case of VTEC in patient we observed.

A man of 53 years old was admitted to the orthopedics department with a diagnosis of right-sided idiopathic deforming coxarthrosis of the 3d degree. Left hip endoprosthesis. Comorbidities are: grade 2 arterial hypertension of high-risk, chronic heart failure 1. Obesity 3. (BMI 46). Diabetes mellitus type 2. Lower extremity varicose vein disease (C3a, S, As, p, d, En). Postthrombophlebitic syndrome of popliteal veins of tibial segment on the left, recanalization. According to duplex sonography symptoms of postthrombophlebitic syndrome of popliteal veins, tibial segment on the left, recanalization. Symptoms of varicose deformation of subcutaneous veins on both sides. Valve regurgitation of the great saphenous vein, tributaries of the great saphenous veins, perforating veins on both sides.

Clinical examination revealed the following TR factors considered above: hypertension, diabetes mellitus type 2, obesity, VDLE, personal history of thrombosis, blood group A (II), hyperhomocysteinemia - 18 μmol/l, Rivermead mobility index 13 points, and the presence of clinically significant depression - 11 points. On the second day after hip replacement the patient, with prophylactic dose (based on body weight - 50 mg per day) of enoxaparin sodium, had pain in the thigh area of the right lower limb, dyspnea at rest, on examination - swelling of the right lower limb to the lower third of the thigh. According to duplex sonography venous thrombosis of iliofemoral-popliteal-pedial segment of the lower extremities on both sides was revealed. According to CT nonmassive pulmonary embolism was verified.

Considering this clinical case it should be noted that there is an evidence that the standard dose of enoxaparin is insufficient for chemoprophylaxis in many patients [23,24].

Conclusion

According to the analysis of the prognostic significance of 26 potential TR factors in terms of modern antithrombotic pharmacoprophylaxis, six of them have been established, which statistically significantly increases the probability of VTEC occurrence after HR. They included type 2 DM, female sex, hypodynamia, the age over 60 years, elevated D-dimers level before surgery, and the presence of VDLE.

Other TR factors, such as hyperglycemia that includes impaired glucose tolerance or type 2 DM, arterial hypertension and obesity, significantly demonstrated themselves only in a combination.

The obtained results allow for selecting patients with very high risk of VTEC and providing an individual approach to thromboprophylaxis, which may include modification (in pre-operative period) of the controlled TR factors (hyperglycemia, hypodynamia, elevation of coagulation blood properties, varicose disease of the lower extremities) or the increase of a dose of the anticoagulant used.

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