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Modern oral medications to prevent venous thromboembolism – critical review of evidence base in terms of a risk/benefit ratio

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Modern oral medications used to prevent venous thromboembolism (VTE) have gained widespread use with major orthopaedic and trauma procedures. There are no accurate multicenter data on the frequency of usage of different prophylactic medications in our country but discussions of the colleagues at specialized web forums make us suspect that factor Xa and dabigatran etexilate inhibitors are in the top three next to low molecular weight heparins. Marketing and promotion strategies of pharmaceutical companies are likely to be of immense importance in that with the contribution of clinical research studies for pharmaceutical drugs. However, preferences of European and American orthopaedic surgeons for the choice of drugs are completely different from those of Russian surgeons. Vitamin K antagonists, acetylsalicylic acid, low molecular weight heparins are commonly used for antithrombotic therapy abroad. Different approaches of Russian and foreign orthopaedic surgeons to the choice of drugs can be explained by a different use of a high-quality evidence base. In our opinion, a collision component can be involved in the endpoints of clinical trials that will be discussed in the present critical review.

Ключевые слова: venous thromboembolism, prophylaxis, arthroplasty, evidence-based medicine, pulmonary embolism

INTRODUCTION

Prevention of venous thromboembolism (VTE) manifested as either deep vein thrombosis (DVT) or pulmonary embolism (PE) is crucial for patients undergoing major orthopaedic surgery including total joint replacement and widely discussed in the world literature. A recent thread of September 26, 2018 at OrthoForum that prompted the author to the critical review focused on utility of a thromboprophylactic strategy on prevention of VTE in immobilization, in an attempt to get the facts straight… [1]. The optimal approach to thromboprophylaxis was discussed at the forum, and with increased patient awareness, there were also legal implications associated with the development of complications. Papers and respective clinical practice guidelines for VTE prophylaxis have been published by professional associations including those published from Russian National Associations:

– Russian clinical practice recommendations "Prophylaxis of venous thromboembolism in traumatology and orthopaedics", 2012 [2];

– Russian clinical practice recommendations on diagnosis, treatment and prevention of deep vein thrombosis, 2015 [3];

– National Standard of the Russian Federation "Prophylaxis of VTE syndromes ", GOST R 56377, 2015 printed out in 31 copies and being available in electronic format [4].

National Standard (GOST R 56377) is not in compliance with Article 76 of Federal Law No. 323-FZ of 21 November 2011 on Basics of Health Protection of the Citizens of the Russian Federation as amended by Federal Laws of 08 March 2015 No. 55-FZ, of 29 December 2015 No.389-FZ 2 but medical practitioners treat the document as bindings due to the extent to which they are influenced by the law because of fear of legal liability in the course of their clinical practice that is not quite reasonable in our opinion.

The Russian guidelines outline prophylaxis strategies identified by the National Institute for Health and Care Excellence (NICE, UK) [5], the Scottish Intercollegiate Guidelines Network (SIGN, Scotland) [6], International Consensus Statement (ICS) [7], National Health and Medical Research Council (NHMRC, Australia) [8], the American College of Chest Physicians (ACCP, USA) [9, 10, 11] and the American Association of Orthopedic Surgery (AAOS, USA) [12]. We believe that the ACCP provides the most adequate guidance for VTE prophylaxis and the 9th edition ACCP guidelines were published in 2012 [9] and generated a lot of

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discussions [13, 14]. Copying guidelines may result in loss of quality. The Russian clinical practice recommendations on diagnosis, treatment and prevention of deep vein thrombosis of 2015 [3] include a one-page trauma section with six references mentioned in the list and with one being pertinent to traumatology [2]. Opinions of medical practitioners from OrthoForum [1] thread appear to be disconcerted with the existing recommendations published six years ago and adopted by expertise council seven years ago, and updated VTE prophylaxis guidelines is needed for trauma patients. Updated recommendations are very likely to replicate foreign guidelines provided the availability of evidence based guidelines for VTE prophylaxis.

Study design as the basis to formulate recommendations

We earlier reported [14] on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach providing a system for rating quality of evidence and strength of recommendations [15]. There are controversies regarding identification/diagnosis of endpoints discussed in the previous publication. Numerous considerations attend the question of which endpoints to use including DVT, proximal DVT and distal DVT, symptomatic and asymptomatic thrombosis. There are also controversies in diagnostic aspects of endpoint detection (ultrasonographic screening, venography) that make the situation more difficult. An identical situation is observed with analysis of PE as an endpoint (symptomatic, asymptomatic, extent of involvement lethal/nonlethal, diagnostic modalities) [14]. Serious adverse events including bleeding (minor, major), stroke are specific conditions to be considered in addition to major endpoints (i.e. VTE complications). Researches on VTE prevention focus primarily on thromboembolic and hemorrhagic complications. Application of ACCP-GRADE approach identifies the so-called "important outcomes" (symptomatic DVT and serious bleeding) having advantages over surrogate criteria (venographic DVT) [16]. The decision on VTE prevention should be based on the risk/benefit ratio. And there is also a question whether the physician is well aware of all risks related to pharmacological VTE prophylaxis using clinical practice recommendations.

As it was noted before, no accurate data on preferences of VTE prophylaxis in orthopaedic procedures are available in the Russian Federation. Telephone questionnaires of the colleagues from the leading joint replacement centers in Moscow with annual surgical activity of more than 1000 procedures indicated to the wide oral administration of rivaroxaban and dabigatran etexilate:

- I.M. Sechenov First Moscow State Medical University: about 100 % of patients receive dabigatran etexilate in some months;
- N.I. Pirogov Russian National Research Medical University: rivaroxaban in 99 %, a low-molecular weight heparin in 1 % (the strategy of the last three years employed for more than 9000 patients);
- Center for Treatment and Rehabilitation: rivaroxaban in 90 %, a low-molecular weight heparin in 10 %.
- S.P.Botkin Moscow City Clinical Hospital: rivaroxaban in 60 %, dabigatran etexilate in 35 %, a low-molecular weight heparin in 5 %.

A separate study is needed to obtain more accurate figures since shifting the management with a low-molecular weight heparin to oral administration is more common as compared to monopharmprophylaxis. In any case, this is not so important for the critical review, however, oral anticoagulation therapy is likely to be more common in Russia than in Europe and North America. The most commonly prescribed postoperative anticoagulation in the USA is warfarin (38.0 %), followed by low-molecular weight heparin (33.8 %) [17].

Rivaroxaban and risk of infection. Risk of infection complications was first reported in 2012. Simon S. Jameson et al. compared 2762 patients who were prescribed rivaroxaban following knee and hip arthroplasty and patients who were prescribed a low-molecular weight heparin. Rivaroxaban group showed a higher rate of superficial wound complications (3.85 % compared with 2.8 %; OR = 0.72, 95 % confidence interval CI = 0.58–0.9; p = 0.005) [18]. In the same year of 2012 Terry Stanton conducted retrospective cohort analysis of 1558 consecutive patients undergoing joint replacement and found [19] that in the first group of 489 patients who received tinzaparin, the rate of wound complications was 1.8 %; the next 559 patients were given rivaroxaban and had the rate of wound complications of 3.94 %

(p = 0.046). Because of the significant increase in the rate of wound complications the final 510 patients received tinzaparin and had a wound complication rate of 1.6 % (p = 0.02 compared with the second group). Summarizing wound complication rate of the first and third groups and comparing it with the second group showed a greater statistical significance in the rise of complication rate in the rivaroxaban group.

In 2013 G.S. Chahal et al. [20] published results of a retrospective cohort study comparing arthroplasty patients who received rivaroxaban (160 patients) and enoxaparin (227 patients). They found that patients who received rivaroxaban were more than twice as likely to return to theater for wound complications compared to patients receiving enoxaparin. Infection rates increased from 0.9 % to 1.9 % after the introduction of rivaroxaban and microbiologically confirmed superficial infections rose from 1.3 % to 3.1 % in rivaroxaban patients. Although not statistically significant, this increase was in line with previous studies. The study highlighted the need for large randomized controlled trials to assess postoperative complications following the introduction of rivaroxaban for post-arthroplasty thromboprophylaxis. In the same year of 2013 K. Sindali et al. reported a tendency of greater risk of infection with the introduction of rivaroxaban (202 patients, complication rate of 5.0 %) as compared to the introduction of enoxaparin (56 patients, complication rate of 1.8 %). The differences were not significant due to a small patient population [21].

By 2015 there were 4 publications reporting the rise in infections with the introduction of rivaroxaban. Two relatively big series reported statistically significant differences [18, 19], and the differences were found insignificant in smaller cohorts [20, 21]. In May 2015 I spoke to A.G.Turpie who developed rivaroxaban study designs for orthopaedic surgery and suggested the importance of endpoints for both superficial and deep surgical site infections with paraprosthetic joint infection being a disaster for the patient and the surgeon. Simon S. Jameson who was the first to report about the increased infection rate supported the consideration. In 2017 Paolo Di Benedetto et al. reported no evidence of association between rivaroxaban and early acute periprosthetic joint infection in the group of 205 patients [22], but the significance of the conclusion seemed to be unconvincing in context with previous publications and the cohort of patients reviewed.

Unfortunately there have been no adequate findings on the risk of infection with the introduction of rivaroxaban by October 2018 and we have high expectations for PEPPER [23], a large clinical trial that started in 2016 and is estimated to be primarily completed in 2020. The PEPPER trial will work with 25,000 (!) patients who are undergoing total knee (TKA) and hip (THA) replacement and findings will be available in 2021. PEPPER trial is quite different from previous trials (XAMOS, etc.) in terms of enrollment, treatment groups and endpoints. The three most commonly used anticoagulants in North America were selected for the trial. The anticoagulants to be compared were acetylsalicylic acid (aspirin), coumadin (vitamin K antagonist, warfarin) and rivaroxaban (xarelto). The trial is expected to shed light on controversial role of the acetylsalicylic acid [13, 14]. No low-molecular weight heparin has been included in the trial.

Most common endpoints are:

– all-cause mortality, clinically important PE and DVP;

– hemorrhagic complications (major, clinically important) including problems of postoperative wound healing leading to reoperation, deep infection;

– joint function assessed with subjective scales;

– quality of life assessed with subjective scales.

Therefore, specific and very important aspects of orthopaedic surgery will be studied exploring superficial and deep infection rate, quality of life of arthroplasty patients and outcomes of joint replacement. One cannot overestimate the importance of PEPPER clinical trial which is ground-breaking prior to obtaining results using important orthopaedic endpoints identified by investigators.

Dabigatran etexilate and risk of infection. There is only one research on dabigatran etexilate reporting somewhat disturbing results. In 2011 S.K. Gill et al. compared dabigatran administered in 56 prospective patients and dalteparin administered in 67 retrospective patients who received acetylsalicylic acid discharged home. The rate of reoperation due to superficial infection was 7 % (n = 4) in dabigatran group and 1 % (n = 1) in dalteparin group. The differences were insignificant due to the small cohort of patients [24].

Study design is known to rely largely on manufacturers. In case of rivaroxaban there is a span of four years between first reports on infections and PEPPER launch. Dabigatran study program on was announced in 2011 and since then there has been no efforts exerted by the manufacturer to explore infection rate after total joint replacement procedures. The problem appears to be important solely for the surgeon and the patient and the manufacturer of dabigatran has made no efforts to provide a sustainable approach to the drug's anticoagulant activity.

Vitamin K antagonist. In 2014 Z. Wang et al. [25] used the Global Orthopedic Registry (GLORY) to review 3,755 patients in US who elected for primary total hip or knee arthroplasty, received either warfarin or low-molecular weight heparin as VTE prophylaxis. Compared to warfarin, low-molecular weight heparin was associated with significantly higher rates of reoperation (2.4 % vs. 1.3 %; OR = 1.77) and infections (1.6 % vs. 0.6 %; OR = 2.79). We introduced the publication (being not a rare occurrence) to show warfarin as one of the most common anticoagulants in US. But warfarin and other oral drugs for VTE prophylaxis have several shortcomings.

Manipulation. There was an interesting article published in Journal of Bone and Joint Surgery August issue 2018. C.A. Kahlenberg et al. [17] analyzed 32,320 patients who underwent a primary total knee replacement. There were 1,178 patients (3.64 %) who underwent manipulation under anesthesia. Comparison with low molecular weight heparin showed a significant increase in the risk of manipulation under anesthesia for patients who received warfarin (hazard ratio, 1.17, $p = 0.032$) and xabans, direct factor Xa inhibitors, (hazard ratio, 1.42, $p < 0.001$), in particular.

CONCLUSION

Appropriate VTE prophylaxis is ensured through standards and recommendations relating to clinical practice issues within orthopaedics, however, clinical guidelines and recommendations of national orthopaedic associations are limited by clinical trials quality filter. Thromboembolism prophylaxis with oral anticoagulants is common in orthopaedic surgery in our country and oral administrations are more common as compared to foreign countries. Risk/benefit ratio is deemed to lack a comprehensive evaluation with less focus on infections in thromboembolism prevention issues. We can't help remembering a brilliant remark from Arkady Raykin, 'Who is the person who has made the suit?' that can be interpreted as "Are there any complaints with thromboembolism complications?' An increased rate of manipulation under anesthesia after total knee replacement has been reported in patients who received direct factor Xa inhibitors. The extensive rivaroxaban clinical trial program involving clinically important primary endpoints in addition to thromboembolism complications represents a significant advance for VTE prophylaxis providing a comprehensive evaluation of the patient and invites genuine respect. There is at least a span of 10 years between the first reports on wound complications following rivaroxaban administration (2012) and clinical evidence to be generated from PEPPER in 2012. There is a lack of scientific evidence of the safety and efficacy of dabigatran with an underestimation of adverse effects. Our national clinical practice recommendations for the prevention of venous thromboembolism require updating revision with information on infections to be included and a tendency to oral anticoagulant administration in orthopaedic surgery that is not in line with the practice in North America to be considered.

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