

Assessment of the effects of low molecular heparins in pulmonary embolism prophylaxis

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ABSTRACT:

Introduction: Pulmonary embolism (PE) is a severe condition that can be the source of significant morbidity and mortality. It is the major complication of venous thromboembolism (VTE) which, by occluding the pulmonary arterial bed may lead to an acute life-threatening state. The clinical management of patients with acute pulmonary embolism has rapidly changed over the years. After the diagnosis of the PE, the anticoagulant and thrombolytic therapy is initiated. Most commonly, low molecular weight heparins (LMWH), unfractionated heparins (UFH), fondaparinux or vitamin K antagonists are used for the anticoagulant therapy. However, LMWH are still uncertain agents, both in the PE prophylaxis and in the high-risk PE cases.

Objective: The aim of the article is to assess the effects of LMWH in the pulmonary embolism prophylaxis.

State of knowledge: A range of clinical and epidemiological studies have shown the relationship between the anticoagulant therapy using the LMWH in the PE prophylaxis. Lower risk of not only PE but also therapy-induced haemorrhages, blood clots and embolisms

recurrences were proven in several meta-analyses. Moreover, the LMWH therapy seems to have a better impact on prevention of VTE symptoms and post-surgical embolisms than other anticoagulant agents. However, some studies have shown that the therapy using LMWH can be replaced with another anticoagulant with a comparable risk of complications.

Conclusion: In the light of this informations, it is surely possible that the LMWH has a better impact in the PE prophylaxis and post-surgical complications prevention than other agents. Still, we can face various results of the studies but the effectiveness of their activity in most cases leaves no doubt for the reasonableness of their usage.

Key words: Pulmonary Embolism, Low Molecular Weight Heparin, Thromboprophylaxis.

Introduction and objective

Pulmonary embolism (PE) with deep vein thrombosis (DVT) combined constitute the elements of venous thromboembolism (VTE). In most of the cases, a thrombus is a material which obstructs the blood flow. It can emerge as a result of a surgical interference (for example in case of major joint, lower limbs or lesser pelvis surgeries) or both acute and chronic diseases (e.g. as a result of chronic heart failure, myocardial infarct, enteritis, nephrotic syndrome, chronic lung failure). Moreover, its emergence can constitute a complication of both pregnancy and postpartum period, oral contraception, excessive obesity or immobility [1,2]. Worth mentioning is the fact that, besides regular thrombi, also amniotic fluid, air, neoplastic masses, adipose tissue or foreign bodies can constitute an embolus [1]. In the treatment of the PE, low molecular weight heparins (LMWH) such as enoxaparin, nadroparin and dalteparin are usually used [3]. Since they can be administered orally, they constitute a better alternative for unfractionated heparins (UFH, standard heparins) which are by standard administered intravenous. Only about 30% of the UFH molecules consist of the pentasaccharide chains which are responsible for their anticoagulative activity. Consequently, in case of the UFH, it is necessary to control their anticoagulative effect [2,4]. Likewise, the immobility of a patient can be a factor contributing to the VTE development which is essential for the intravenous UFH administration [1].

For the patients with diagnosed VTE an initial treatment up to 3 months should be induced. The LMWH, other oral anticoagulants except vitamin K antagonists (such as rivaroxaban, apixaban and dabigatran), fondaparinux or HNF are used for the therapy [1]. As far as the PE is concerned, the anticoagulant therapy should last as long as in the case of the DVT. In patients with the low- and moderate-risk PE, the anticoagulant therapy is based on the UFH or the LMWH dosage. It was proven that the UFH usage reduces the risk of early death by 70% comparing to no use [5, 6]. However, in patients with the high-risk PE, besides the symptomatic (alignment of hemodynamic disorders) and anticoagulant treatment, the thrombolytic treatment using the streptokinase or the alteplase should be induced [1,7].

Nowadays, according to the British National Formulary (BNF) and National Institute for Health and Care Excellence (NICE) recommendations, the LMWH are used for the thromboprophylaxis of the VTE and the DVT in patients from the risk groups, such as the surgical or orthopaedical patients. Besides them, this kind of prophylaxis should be induced in pregnant women, patients with acute coronary syndrome or extracorporeal circulation to prevent the thrombi formation [3].

The effects of heparins activity contain antithrombin activation, the role of which is thrombin and other serine proteases inhibition. To achieve it, it is necessary to form a ternary complex composed of heparin, antithrombin and thrombin. It is the pentasaccharide structure inside the heparin molecule which can initiate the change of molecular conformation which makes possible to activate the antithrombin. As far as the UFH are concerned, in their molecules, more low molecular monomers (18 at least) than in case of LMWH can be

observed, whereby their binding with thrombin and heparin-antithrombin-thrombin complex creation is facilitated. Thereby, the UFH manifest their tendencies to affect not only the thrombin, but also the coagulation factor Xa, while the LMWH most effectively inhibit only the factor Xa. As far as the molecular structure of both types of heparins is concerned, the LMWH manifest more pentasaccharide structures than the UFH do. As a result, the anticoagulant effect of the LMWH is more predictable than in the case of the UFH [4,8]. This molecular difference results in no need for its constant monitoring in patients who need to undergo the anticoagulant treatment and the thromboprophylaxis [1].

The basic risk scales used to stratify the anticoagulant treatment, especially in the patients with atrial fibrillation incidences (which can be a significant risk factor of systemic thromboembolism) are the CHA₂DS₂-VASc scale and the HAS-BLED scale. The CHA₂DS₂-VASc scale serves to assess the risk of thromboembolic complications in patients with atrial fibrillation. The scale allows the indication of patients with atrial fibrillation, in whom it is necessary to implement antiplatelet or antithrombotic therapy. The assessment is based on the thromboembolic incidents risk factors analysis, such as a congestive heart failure, hypertension, age (≥ 75 years), diabetes mellitus, transient ischaemic attack, a vascular disease, sex category (female). The CHA₂DS₂-VASc scale is an improvement of the CHADS₂ scale, which extends the latter by additional risk factors for thromboembolic complications, such as previously mentioned vascular diseases. Nowadays, this scale is recommended to assess the risk of stroke in nonvalvular atrial fibrillation [9]. As far as the HAS-BLED scale is concerned, it refers to the bleeding risk assessment in patients with atrial fibrillation who have been given the antithrombotic therapy using the vitamin K antagonists. Several parameters are evaluated with this scale, such as hypertension (systolic blood pressure >160 mmHg), abnormal renal or liver function, stroke incidents, bleeding predisposition, labile International Normalized Ratio, elderly, drugs and alcohol usage [10].

The actual LMWH effect, the optimal dose and their advantage of activity over, most of all, the UFH or other forms of pharmacological methods of anticoagulant prophylaxis (such as the selective factor Xa inhibitors, the vitamin K antagonists or the thrombin inhibitors [1]) remains the constant subject of many discussions [11]. The aim of the article was to exhibit the effect of anticoagulant therapy using the LMWH in the PE prophylaxis. The articles were collected using the PubMed database - the research was performed from October 2018 to February 2019. The assessment was based on the comparison between the LMWH and other anticoagulant agents therapies.

Description of the state of knowledge

LMWH compared to other anticoagulants. Compared to the UFH activity, the LMWH manifest longer half-life time in the serum, since the UFH is rapidly neutralised by the platelet factor 4. Moreover, there is no need for the laboratory monitoring of their anticoagulant effect, they have an insignificant effect on the platelets activity and they can be administered in a dose based on body weight [1,12]. The LMWH have a significant impact on decreasing the mortality rate in acute DVT patients. As far as the massive hemorrhages complications are concerned, the odds ratio determination demonstrated the statistically insignificant predominance of the LMWH over the UFH. Furthermore, both the LMWH and the UFH turned out to have a similar effect as far as the preventing the blood clots recurrence is concerned [13]. The results of the examinations allow to state that the administration of the constant doses of the UFH with no monitoring can lead to similar effects just like the administration of the constant doses of the LMWH [12]. Based on the results of a meta-analysis which was conducted among 2210 patients with the PE, comparing to the UFH, the LMWH seemed to result in statistically insignificant decrease in incidences of the recurrent, symptomatic PE. Regarding the complications in the form of bleeding, the odds ratio was in

favor of the LMWH, it was still statistically insignificant though [14].

Comparing to the vitamin K antagonists, analyzing the anticoagulant therapy of 1379 patients, the statistically insignificant decrease in the VTE and the massive bleeding incidents in favor of the LMWH was proven. Moreover, no significant differences in a general mortality were revealed, regardless of the induced therapy [15]. In a similar meta-analysis, comparing the treatment of 3197 patients, there was again an insignificant decrease in the PE incidents demonstrated. For all the conducted examinations together, there was a minor impact on the bleeding occurrence in favor of the LMWH comparing to oral anticoagulants. Likewise, there were no significant differences in mortality [5]. Worth mentioning is the fact that the LMWH use, except for no significant differences in VTE or mortality risk decreasing, exclude the necessity for a constant laboratory monitoring of their anticoagulant effect (comparing to vitamin K antagonists) and their usage induces a decrease in risk of bleeding incidences. Moreover, the vitamin K antagonists constitute the agents causing allergic reactions for certain patients. Consequently, their usage can lead to a certain risk of incidences of sensitiveness [5]. Certainly, more experiments should be conducted to clearly demonstrate the predominance of the LMWH over the oral anticoagulants.

The Non-vitamin K antagonist oral anticoagulants (NOAC) comprise drugs such as dabigatran (direct competitive and reversible thrombin inhibitor), rivaroxaban and apixaban (direct, selective and reversible factor Xa inhibitors). They are mostly recommended in indicated in the primary prevention of thromboembolic events after knee and hip arthroplasty [4]. However, there are several factors which make slower the adoption of these agents into the clinical practice including concerns regarding the drug's adherence without laboratory monitoring, some uncertainties about dosing in specific patient populations (e.g., in patients with renal dysfunction, marked extremes of body weight), and also higher drug costs in comparison with warfarin [16]. A meta analysis comparing the LMWH and the apixaban was conducted - the results were based on the thromboprophylaxis induced in 11828 patients. In comparison with the NOAC, the LMWH showed a significantly higher risk of VTE events and overall mortality combined. Conversely, the lower risk of major VTE events, or of symptomatic VTE events and VTE-related mortality combined was not observed in case of the apixaban usage. The statistical analysis demonstrate that in patients after the knee or hip replacement surgery, in the thromboprophylaxis, apixaban seems equally effective and safe to LMWH twice a day. However, when compared with apixaban once a day, the LMWH seem to be a worse option of antithrombotic prophylaxis [17].

The American Academy of Orthopaedic Surgeons' recommendation is that the duration and the choice of the thromboprophylaxis should be decided by the treating surgeon. The results of an observational study, based on the outcomes of the thromboprophylaxis conducted using different policies in patients after hip and knee replacements revealed that there is no specific differences in outcomes for either LMWH or NOAC in the mortality, thromboembolic complications, emergency readmission, and bleeding rates. This studies seem to confirm the recommendations mentioned above [18]. As far as the specific agents' side effects are concerned, a systematic review and meta-analysis of randomized controlled trials of venous thromboprophylaxis in patients after total joint arthroplasty revealed that in case of LMWH usage, there was a significantly increased relative risk of surgical site bleeding in comparison with control and warfarin usage. Nevertheless, the relative risk of LMWH trended higher than apixaban and was similar to rivaroxaban [19].

The acetylsalicylic acid (ASA) is an agent which is often used in the thromboprophylaxis. Given the results of a randomised controlled trial (RCT), there was showed no evident difference in rates of VTE incidents in patients who were given ASA or LMWH following total hip and knee arthroplasty [20]. Besides clinical equipoise when ASA is compared with other anticoagulants, studies conducted specifically in

orthopaedic surgery patients' results suggest that ASA seems to be as effective as low molecular weight heparin (LMWH) and, what is more, it may reduce bleeding risk [21]. Moreover, it was demonstrated that, in the patients suffering from the multiple myeloma, except its undoubted significant effect in the thromboprophylaxis comparing to the placebo or lack of treatment, there was no meaningful superiority of the ASA usage over the LMWH. [22].

It turns out that in most of the cases the data leaves no doubt in the thromboprophylaxis in favor of the LMWH. Nevertheless, there is still not enough information, often contradictory, which would clearly state the superiority of a particular thromboprophylaxis method over the others.

LMWH at the VTE therapy. The quality of the thromboprophylaxis with the LMWH usage towards the risk of VTE incidence was the subject of a great number of clinical trials and meta-analyses. Compared with the use of placebo or discontinuation of any therapy, according to the meta-analysis of the LMWH effect in the prevention of VTE in surgical practice, it was demonstrated that the LMWH had a significant impact in reducing the number of cases of asymptomatic deep vein thrombosis. It was conjugated with a significant reduction in the incidence of both pulmonary thrombosis and clinically confirmed VTE, with a significant decrease in overall mortality due to complications of these diseases [11].

In the study, aim of which was to determine the quality of anticoagulant prophylaxis with the LMWH usage, the data of 12352 outpatients who received chemotherapy was collected. As demonstrated, the primary anticoagulant prophylaxis used with the LMWH resulted in a reduction in the incidence of symptomatic VTE compared to a group of patients for whom such prophylaxis was not used [23]. According to similar studies, the LMWH has also been shown to reduce the symptomatic VTE as well as the PE in patients receiving chemotherapy, which is most evident in the group of patients suffering from pancreatic and lung cancer. It has been suggested that the use of the LMWH in the thromboprophylaxis in these two groups of patients should be an action especially taken into account [24]. As far as the oncological patients are concerned, the LMWH is preferred to unfractionated heparins or vitamin K antagonists for the after-surgery prophylaxis, or for secondary prevention after the occurrence of a VTE incident that could be associated with neoplastic disease [25]. A similar relationship was observed among trauma patients - the use of the LMWH was combined with a reduction of complications in the form of VTE [26]. Another study showed that among patients who underwent the surgical procedure of high ligation and stripping of the great saphenous vein, the use of HDCz at doses of 6,000 IU once a day or 4,000 IU twice a day did not bring much benefit in reducing the prevalence of VTE. The results were compared to prophylaxis conducted with the use of subcutaneously administered unfractionated heparin at a dose of 125 U / kg / day or in comparison to not using any prophylaxis [27]. Similarly, among patients after hip fracture surgery, no significant difference in the reduction of VTE was noticed either [28]. Additionally, in patients after knee arthroscopy, the ineffectiveness of any thromboprophylaxis was demonstrated [29].

LMWH at the PE therapy. It is worth to present the results of research on 153474 patients after various serious injuries in which the thromboprophylaxis with the use of the unfractionated heparins or the low molecular weight heparins was carried out. As it turned out, regardless of the type of injury, patients treated with the LMWH had lower rates of pulmonary embolism incidences than those treated with UFH. In addition, in the trauma centers using the LMWH most often, the incidence of complications in the form of the PE was significantly lower than in others using mainly UFH. The results of this analysis significantly support the use of HDCz for the prevention of thrombi formation in patients with high injuries [30].

Orthopedic patients constitute a group in which a significantly higher VTE detection rate is observed as a complication of the operation [31]. In the analysis based on the results of

7983 patients who underwent elective total hip arthroplasty and were treated using the LMWH thromboprophylaxis, warfarin or aspirin, it was demonstrated that the use of the LMWH did not result in a reduction in the incidence of the PE. It even resulted in an increase in the mortality, as compared to the incidence and mortality in groups of patients who were treated with other types of anticoagulant prophylaxis [32].

In the next analysis, the results of a total of 3,680 patients were analyzed. The examined patients experienced immobilisation of the lower limb by a plaster cast or a brace - an important risk factor for the development of deep vein thrombosis, which may result in pulmonary thrombosis. In the case of patients who did not have any anticoagulant prophylaxis performed, the DVT occurred in 4.3% to 40% of cases. In patients who underwent the thromboprophylaxis with the LMWH, the percentage of the DVT incidents was significantly lower. The studies between control groups and groups of patients who underwent the thromboprophylaxis using the LMWH showed also no significant effect on the formation of the PE alone. Nevertheless, patients treated with the LMWH had fewer VTE-related symptoms than patients who had no such prophylaxis [33].

Worth marking is the topic of caesarean section surgery, as it is an important risk factor for the development of the VTE and the PE. For the purpose of anticoagulant prophylaxis in such patients, enoxaparin (as one of low molecular weight heparins) is often used. However, there is still an uncertainty about the safety of its administration immediately after cesarean surgery compared to the initiation of its administration after a longer time, especially in the presence of an epidural catheter. According to the studies conducted on 578 patients (328 of whom had epidural analgesia, and 250 were not) during which enoxaparin was administered as soon as 24 hours after the surgery, no spinal epidural hematoma was observed in any patient (which is a rare but serious complication of an epidural anesthesia [34]). One case of low-risk pulmonary embolism and one case of asymptomatic deep-vein thrombosis was observed. Subcutaneous bleeding or wounds were reported in a small percentage of cases. This study gives indications the reasonableness of enoxaparin administration in the first hours after the caesarean section [35].

Regarding patients with an acute ischemic stroke, the VTE or the PE can be a complication of which (this phenomenon is still not well understood and described though [36, 37]), a meta-analysis was performed in which the total results of 23043 patients after the acute ischemic infarct were included. It was demonstrated that the use of the UFH at high doses resulted in a reduction of cases (compared to the control sample) of pulmonary thrombosis, however, this was combined with an increased incidence of intracranial and extra-valvular haemorrhage. The use of UFH at low doses ($\leq 15,000$ IU / day) did not affect the detection of pulmonary thrombosis. The incidence of intracranial or extracranial haemorrhage was not significantly increased. High doses of the LMWH reduced the occurrence of both deep vein thrombosis and pulmonary thrombosis, however, they also increased the incidence of intracranial and extracranial haemorrhages. Furthermore, the LMWH at low doses ($\leq 6,000$ IU / day) reduced the incidence of both ailments, with the absence of an increased risk of intracranial and extracranial haemorrhage. Concluding, the low-doses of the LMWH ($\leq 6,000$ IU / day) have the best effect in patients with acute ischemic stroke, both in the prevention of the deep vein thrombosis and the pulmonary thrombosis, while not having a major impact on the occurrence of intra- or extracranial haemorrhages [37].

In patients with lung cancer treated surgically, it was demonstrated that the use of a chemical anticoagulant prophylaxis with low molecular weight heparins resulted in a slightly higher, though statistically insignificant increase in the incidence of pulmonary thrombosis as a complication of the operation, compared to patients in whom no type of pharmacological prophylaxis was used [38].

Finally, worth singling out would be an example of the data made within twenty years

(1995-2105) based on the results of 34764 patients after hip arthroplasty, who, divided into groups, underwent thromboprophylaxis with the LMWH, oral factor Xa inhibitors of the coagulation cascade, oral thrombin inhibitors, inhibitors of Xa/IIa factors, aspirin or warfarin. It has been shown that, despite the relatively low occurrence of complications in the form of pulmonary embolism (~ 0.21%), this is a condition that is invariably present (its prevalence remained constant over the years 1997-2013). This can suggest that in a certain group of patients, despite the use of aggressive anticoagulant prophylaxis, regardless of its type, there could be some genetic predispositions to the formation of blood clots [39].

Summary

Pulmonary thrombosis is a disorder that carries a significant risk of mortality. It is important, therefore, that in risk groups, the thromboprophylaxis should be carried out as quickly and as effectively as possible. Many studies and meta-analyses have been performed to compare its quality, conducting it with the LMWH or with the use of other anticoagulants in order to prevent the development of VTE, DVT and the PE itself. It turns out, however, that individual studies are not completely compatible with each other. There are many results that testify of the advantage of the LMWH over other anticoagulants in form of vitamin K antagonists, aspirin and unfractionated heparins alone [5, 14, 15, 22]. Nevertheless, there can be several studies that show no specific superiority of the LMWH usage over other anticoagulants [17, 18, 19, 20, 21]. The effectiveness of the studied group of drugs in the prophylaxis of VTE is often observed among patients receiving chemotherapy, trauma patients, those experiencing limb immobilization or after an acute ischemic stroke incident [11, 24, 31, 32, 33, 34, 37]. In addition, in the prophylaxis of the PE, the LMWH efficacy is observed among trauma patients, patients after cesarean surgery or those after an acute ischemic stroke incidents [30, 35, 37]. Despite this, one can find the results of studies that do not show a significant advantage of the LMWH in the thromboprophylaxis. Such regularities occur in the results of examinations, among others, in patients after high ligation and stripping of the great saphenous vein, hip fracture surgery and after knee arthroscopy [23, 27, 28, 35, 36]. One of the studies indicated the harmfulness of such an anticoagulant prophylaxis method [38]. It turns out, therefore, that the results of individual studies are incompatible with each other, depending on the group of patients being examined and the circumstances of anticoagulation prophylaxis. This regularity is observed not only for the pulmonary thrombosis itself, the quality of treatment conducted with their use also compared for other disease entities - VTE and DVT. However, anticoagulation prophylaxis with the use of low molecular weight heparins became a gold standard implemented among many groups of patients. It is necessary to extend the research to include more groups, nevertheless the effectiveness of their activity in most cases leaves no doubt, and the research seems to confirm this to a large extent.

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