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Prevention of pulmonary embolism through the prism of Systematic reviews and meta-analyses

Prevención de la embolia pulmonar a través del prisma de las revisiones sistemáticas y los meta-análisis

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ABSTRACT

Introduction: The prevention of pulmonary embolism is a subject of ongoing debate, with significant ambiguity and controversy surrounding current methods. **Objective:** The purpose of this study was to review the modern world literature, focusing exclusively on scientific articles, systematic reviews and meta-analyses published between 2020 and 2023, to assess the effectiveness of various pulmonary embolism prevention strategies. **Methods:** A comprehensive literature search was conducted using leading databases such as Google Scholar, Cochrane Library, EMBASE, EmCare, MEDLINE, EBSCOhost, Web of Science, Ovid Medline, and PubMed. The search strategy was guided by the PRISMA. **Results:** The analysis revealed substantial variability and ambiguity in the effectiveness of pharmacological and mechanical methods for PE prevention. Pharmacological interventions like low molecular weight heparin were effective in certain contexts but inconsistent overall. Mechanical methods, such as intermittent pneumatic compression and venous cava filters, showed mixed results across different patient populations. **Conclusion:** The combined use of pharmacological and mechanical methods sometimes improved outcomes, but the overall evidence was weak and often biased. It is necessary to conduct a larger number of studies, such as randomized controlled trials, with minimizing the level of methodological bias on the mentioned set of means of preventing pulmonary embolism. This should be done in order to eliminate the controversial and ambiguous nature of the means of preventing pulmonary embolism in the research environment.

Key words: pulmonary embolisms, pharmacologic actions, medicine, healthcare system.

RESUMEN

Introducción: La prevención de la embolia pulmonar es un tema de debate continuo, con una ambigüedad y controversia significativas en torno a los métodos actuales. **Objetivo:** El propósito de este estudio fue revisar la literatura mundial moderna, centrándose exclusivamente en artículos científicos, revisiones sistemáticas y metanálisis publicados entre 2020 y 2023, para evaluar la efectividad de varias estrategias de prevención de la embolia pulmonar. **Métodos:** Se realizó una búsqueda bibliográfica exhaustiva utilizando bases de datos líderes como Google Scholar, Cochrane Library, EMBASE, EmCare, MEDLINE, EBSCOhost, Web of Science, Ovid Medline y PubMed. La estrategia de búsqueda fue guiada por PRISMA. **Resultados:** El análisis reveló una variabilidad y ambigüedad sustanciales en la efectividad de los métodos farmacológicos y mecánicos para la prevención de la EP. Las intervenciones farmacológicas como la heparina de bajo peso molecular fueron efectivas en ciertos contextos, pero inconsistentes en general. Los métodos mecánicos, como la compresión neumática intermitente y los filtros venosos cavas, mostraron resultados mixtos en diferentes poblaciones de pacientes. **Conclusión:** El uso combinado de métodos farmacológicos y mecánicos a veces mejoró los resultados, pero la evidencia general fue débil y a menudo sesgada. Es necesario realizar un mayor número de estudios, como ensayos controlados aleatorizados, que minimicen el nivel de sesgo metodológico en el conjunto mencionado de medios para prevenir la embolia pulmonar. Esto debe hacerse con el fin de eliminar la naturaleza controvertida y ambigua de los medios para prevenir la embolia pulmonar en el entorno de la investigación..

Palabras clave: embolismos pulmonares, acciones farmacológicas, medicina, sistema de atención de la salud

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INTRODUCTION

Pulmonary embolism (PE), along with deep vein thrombosis (DVT), is part of the structure of venous thromboembolism (VTE). 10 million cases of the disease are registered in the world per year, 500,000 deaths, in the absence of thromboprophylaxis. The prevalence of VTE in hospital patients ranges from ten to forty percent. In the USA per year, VTE costs 7-10 billion US dollars.[1]

PE is a blockage of the pulmonary artery or its branches, usually by a blood clot that comes from elsewhere in the body. PE is often a sequel of DVT, a type of VTE that develops in the leg, thigh or pelvis[2]. It is a potentially debilitating condition, with a tendency to recur, the third leading cause of adult cardiovascular deaths worldwide, and

a significant burden on healthcare systems and society[3]. About 10 million VTE cases are reported globally every year, half of them is fatal. In hospitalized patients, VTE is often a complication of surgery, with an estimated incidence of 10–40%. PE is thought to account for up to 10% of in-hospital deaths[4,5]. It usually originates in the vascular system of the lower extremities, and the transition to the pulmonary artery is carried out mainly through the inferior vena cava (IVC).

Stasis, hypercoagulability and endothelial damage, collectively known as Virchow's triad, promote thrombosis and can all come into play in a hospital setting[6]. Surgery itself, especially orthopedic, vascular and gynecological, is a major risk factor for VTE and PE, as it induces inflammatory response and activates coagulation pathways. Prolonged immobilization, including during surgery, slows blood circulation and thus contributes to VTE; although ERAS Society guidelines emphasize the importance of early mobilization, weakness, traumatic injuries and obesity, may prevent the patient from being active. The risk of VTE increases for patients with comorbidities, especially past or active cancer, inherited thrombophilias (factor V Leiden, deficiencies of proteins C and S, deficiency of antithrombin III), cardiovascular and autoimmune conditions.[7]

It should be noted that PE as a formidable complication of VTE is considered a potentially preventable disease in hospital patients. Adequate perioperative prophylaxis based on risk stratification can help avert complications, improve patient outcomes and reduce costs. It is important to predict the risks of PE[4] in conditions such as oncology, thoracic surgery, spinal surgery, ischemic stroke, traumatology and orthopedic surgery.

The next measure after the prediction is the prevention of PE. For example, if thromboprophylaxis is not performed after abdominal surgery, the risk of PE increases to 25 percent[8]. The literature mentions a set of means of preventing PE: pharmacological, mechanical, namely, intermittent pneumatic compression, graduated compression stockings and venous cava filters.

Methods for PE prophylaxis can be grouped into pharmacological and mechanical. Pharmacological prophylaxis is the use of low molecular weight heparin (LMWH), unfractionated heparin (UFH), and direct oral anticoagulants (DOACs). Mechanical prophylaxis encompasses the use of inferior vena cava (IVC) filters, intermittent pneumatic compression devices and graduated compression stockings.

Heparins are routinely administered to hospitalized patients to reduce the risk of thrombotic events. UFH is a mixture of different molecular weight heparin fractions. It exerts its anticoagulation effects by forming a complex with antithrombin and thus inhibiting several coagulation factors, including IXa, Xa, XIa, XIIa, and thrombin[9]. LMWH consists of shorter molecules that can bind to antithrombin only, resulting in the inactivation of Xa. UFH has a shorter half-life and a less predictable pharmacokinetics, requiring constant patient monitoring. LMWH is thought to be more effective in preventing thrombotic complications and have a better safety profile, i.e. cause less bleeding and heparin-induced thrombocytopenia. However, reports of the effects of pharmacological prophylaxis are somewhat conflicting. High-risk patients who do not respond well to pharmacological prophylaxes can be offered an IVC placement procedure.

IVC filters are small endovascular umbrella-shaped devices made of biocompatible MRI-friendly alloys or the absorbable polymer polydioxanone. They are placed in the inferior vena cava, which drains venous blood from the lower body and the abdomen into the right atrium, and act like a trap for blood clots, preventing them from traveling up to the pulmonary artery. An IVC filter is inserted into the jugular or femoral vein under image guidance and then advanced to the inferior vena cava[10.] The procedure is minimally invasive and can be performed under moderate sedation or local anesthesia, although some patients may require general anesthesia. Once the patient has returned to their baseline risk level, the filter can be retrieved. Possible complications include procedural complications during placement and retrieval, filter migration or breakage, perforation of the vascular wall and filter thrombosis.

Intermittent pneumatic compression (IPC) devices are inflatable cuffs or sleeves worn around the legs8. Air is pumped into the sleeves at regular time intervals, causing them to inflate and deflate and thus deliver controlled pressure to the veins, mimicking muscle contraction and improving venous return to the heart. IPC devices are also used to stimulate lymphatic drainage and were previously shown to enhance tissue healing. However, they interfere with early mobilization, since they cannot be worn when ambulating. Their noise can annoy the patient or prevent them from sleeping. IPCs can also cause discomfort in the legs and skin irritation.

Graduated compression stockings (GCS) are a cheap alternative to IPC. They apply gradient pressure to the legs, with the highest degree of compression at the ankle, and can be worn at rest or when ambulating. They have relatively few contraindications but noncompliance may be as high as 65%.[11]

Despite the relevance of the prevention of PE, many aspects remain controversial. This is very well stated in the Cochrane Systematic Database[9,12]. We note that the Cochrane systematic reviews along with meta-analyses form the core or apex of evidence-based medicine. Along the way, we also

note the fact that there are no studies based on data from systematic reviews and meta-analyses on the prevention of PE, especially in post-Soviet countries.

The purpose of our study was to review the modern world literature, presented only by systematic reviews and meta-analyses, published over the past few years and devoted to the problem of prevention of PE.

METHODOLOGY

The two types of literature reviews that formed the basis for our article are systematic review and meta-analysis, in which the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol is always the strategy for searching literary data. The main reasons why we decided to rely on data from systematic reviews and meta-analyses is that these two types of reviews form the core of evidence-based medicine, and the second reason is the narrow focus of the research question, unlike the traditional descriptive literary review.

At the first stage of our research, the identification stage, we identified such search databases as Google Scholar, Cochrane Library, EMBASE, EmCare, MEDLINE, EBSCOhost, Web of Science, Ovid Medline, Pubmed. At this stage, data selection was based on keywords such as pulmonary embolism, drug prevention, mechanical prevention, systematic review and meta-analysis. At the second stage, the screening stage, the data selection was based on the title and annotation of the articles.

At the third stage, the stage of more detailed selection and screening, the selection of data was based on inclusion and exclusion criteria as well as on the involvement of two independent specialists. It was important for us to identify articles that, among other things, were written in English over the past few years from 2020 to 2023 and were based on a correct methodological platform.

At the fourth stage, the stage of forming the final list, scientific articles, systematic reviews and meta-analyses were identified, which compiled a list of sources of our research and which were subsequently exposed to synthesis and analysis methods in order to obtain results and conclusions. Finally, this list includes English language 12 systematic reviews and meta-analyses with publication from 2020 to 2023.

The first systematic review covers 12 studies and over 130,000 patients. The second was 51 studies, in 37 of which the sample of patients ranged from 70 to 1,099,093, and in 14 from 148 to 19,217. The third-14 studies and 1914 patients. The fourth was 2 studies and 639 patients. The fifth one consisted of 2 studies and 288 patients. The sixth was 13 studies and 6857 patients. The seventh was 5 studies and 7,515 patients. The eighth was 22 studies and 9072 patients. The ninth one consisted of 8 studies and 3,818 patients. The tenth was 18 studies and 2,474 patients. The eleventh was 10 studies and 718 patients. The twelfth was 10 studies and 47,140 patients. As a result, 11 systematic reviews and meta-analyses covered 167 studies and 210,435 patients, and in the additional, that is the second systematic review and meta-analysis, it is not possible to calculate the exact number of patients.

FINDINGS OF INTERPRETATION

PE prediction

According to a systematic review and meta-analysis of 12 studies and over 130,000 patients, the Caprini, Padua, and IMPROVE scales have a high ability to predict the probability of PE.[1]

On the other hand, according to a systematic review and meta-analysis of 51 studies (in 37 of which the patient sample ranged from 70 to 1,099,093, and in 14 from 148 to 19,217) and 24 prognostic scales (including the most popular Caprini scale), the scales generally have low prognostic potential with a very wide statistical spread from twelve to one hundred percent in terms of sensitivity and from seven point two to one hundred percent in terms of specificity. The second problem is the high degree of methodological bias in most of the studies.[4]

PE prevention

A systematic review and meta-analysis of 13 RCTs and 6857 patients with limb immobilization due to injuries showed the effectiveness of low molecular weight heparin (LMWH) for the prevention of PE (odds ratio [OR]: 0.16; 95% confidence interval [CI]: 0.01-0.74), but the uncertainty of the use of fondaparinux ([OR]: 0.40; 95% [CI]: 0.01-7.53).[13]

However, in the modern literature, there is also information about the lack of effectiveness of the use of LMWH. For example, in the Cochrane systematic review and meta-analysis of 2 studies and 288 patients, no difference was found in the use of chemoprophylaxis (and its absence) of PE in patients with extensive amputations of the lower extremities when using heparin compared with placebo ([OR] 0.84, 95% [CI] 0.35 up to 2.01). According to Cochrane researchers, the level of evidence was low with a high risk of methodological bias.[9]

The second means of preventing PE is considered to be the use of mechanical prophylaxis-intermittent pneumatic compression (IPC). A systematic review and meta-analysis of 5 studies and 7,515 neurosurgical patients showed satisfactory statistics for reducing cases of PE in these patients ([OR] 0.42 [0.25, 0.70], $p < 0.001$; I2: 80%). On the other hand, an unsatisfactory level of evidence for the use

of IPC for the prevention of PE has been shown[14]. However, uncertainty surrounding the effectiveness of the use of IPC for the prevention of PE in 9072 patients requiring thoracic surgery, mainly on the lungs and esophagus, was noted in a systematic review and meta-analysis of 22 studies.[15]

As for the comparison of options within mechanical prophylaxis, in a systematic review and meta–analysis of 14 studies and 1914 patients with surgical diseases of the abdominal region or pelvic organs, it was not proved that IPC, compared with graduated compression stockings (GCS), has improved prevention of PE ([OR] 0.9; 95% CI 0.24-3.36). It should be noted the low level of evidence and the high risk of methodological bias of the studies included in this review and meta-analysis.[8]

Comparisons of mechanical and drug prophylaxis of PE in patients of different cohorts are relevant. In comparative studies, there is evidence of a lack of benefits of either mechanical or drug prophylaxis, so there was no difference between the use of IPC and LMWH (hazard ratio [HR] 1.00, 95% [CI] 0.14 to 7.05) with a low level of evidence in the Cochrane Systematic Review and meta-analysis of 8 studies and 3,818 patients requiring knee arthroscopy.[16]

There are systematic reviews and meta-analyses that provide comparisons on the effectiveness of combined prevention with the use of mechanical and medicinal products. In a systematic review and meta–analysis of 13 studies and 1914 patients with surgical diseases of the abdominal region or pelvic organs, an improvement in the prevention of PE was noted when combining IPC with medications ([OR] 0.25; 95% [CI] 0.09–0.74) or with GCS ([OR] 0.45; 95% [CI] 0.23-0.91).[8]

At the same time, it should be noted the low level of evidence and the high risk of methodological bias in research. If a number of studies indicate an improvement in the prevention of PE by combining mechanical and medicinal agents in patients of various profiles, then the lack of improvement in combined prevention of PE with the use of IPC (risk coefficient [RC], 0.41; 95% [CI], 0.26-0.60) and anticoagulants ([RC] 0.48; 95% [CI], 0.28-0.68) in the comparison with placebo is presented in a systematic review and meta-analysis of 18 studies and 2474 neurosurgical patients. The level of evidence varied from satisfactory to good.[17]

Venous cava filters are considered to be another option for the mechanical prevention of PE.In a systematic review and meta-analysis of 10 studies and 718 cases of the use of cava filters in patients who underwent surgical orthopedic interventions, the effectiveness of cava filters (on a permanent and temporary basis in approximately the same amount, and absorbed 0.6%) in the prevention of PE was shown. In particular, 415 cava filters were applied to 405 high-risk patients, nonfatal PE was observed in 1.5% of cases, and fatal in 0.01% of cases.[10]

Here are the results of another systematic review and meta-analysis covering 10 studies, 7 of which were observational, which included 46,830 trauma patients. In these observational studies, the effectiveness of cava filters in the prevention of PE was proven ([HR] 0.25; 95% [CI], 0.12-0.55). But, on the other hand, in 3 RCTs, which included 310 patients also of a traumatological profile, no such preventive improvement was recorded ([HR], 0.27; 95% [CI], 0.06-1.28). It should be noted that in both cases the level of evidence was low.[18]

And according to the Cochrane Systematic Review and meta-analysis of 2 studies and 639 patients, the use of preventive temporary cava filters in combination with anticoagulants compared only with anticoagulants and in combination with anticoagulants plus IPC compared only with anticoagulants plus IPC, had no difference in both the first case ([RC] 1.74 (0.52 to 5.86) and in the second (the risk coefficient is 0.07 (0.00 to 1.18) with an average level of evidence. In addition, the same systematic review and meta-analysis included 4 studies with 749 patients of different profiles, but the authors were unable to draw clear conclusions about the prospects of using cava filters for the prevention of PE.[12]

The choice of thromboprophylaxis in hospitalized patients depends on several factors, primarily on the patient's risk of VTE, mobility status, and specific clinical circumstances, including equipment availability. Patients with comorbidities, especially cancer, old patients and those temporarily immobilized, are at greater risk for VTE. Orthopedic surgery is associated with higher risk of VTE, including PE, and may require more aggressive thromboprophylaxis.

LMWHs are considered the first-line pharmacological option for thromboprophylaxis, especially in high-risk patients. However, the data on their effectiveness is conflicting, partly due to the lack of adequate statistics on VTE in some patient cohorts[15]. Literature analysis shows that pharmacological thromboprophylaxis in adult patients with injury-induced lower limb immobilization is associated with reduced risk of PE and symptomatic DVT[13]. At the same time, RCTs do not show a significant reduction in the risk of PE or symptomatic DVT following LMWH therapy, compared with a placebo, in healthy patients undergoing orthopedic surgery16. Its effect on bleeding is uncertain. Still, LMWH is more effective in reducing symptomatic DVT than graduated compression stockings. The lack of adequate reporting of complications, including bleeding, varying duration of pharmacological prophylaxis and its use in combination with mechanical thromboprophylaxis, preclude definitive conclusions.[15]

Patients who cannot receive anticoagulation or are at high risk for bleeding may benefit from IVC filters. While their use may be associated with a reduced incidence of PE in high-risk trauma or ultra-high risk orthopedic patients with contraindications to anticoagulation, there are concerns about possible complications, including filter migration, fracture, and thrombosis. IVC filters may have limited effectiveness for DVT prevention[12]. Although there is some evidence that IVC filters effectively prevent fatal PE[10], studies included in the analyzed reviews were mostly observational, poor quality, with small patient cohorts and limited follow-up.[10,18]

Thorough risk-benefit assessment should be recommended prior to using an IVC filter. While IPC may be associated with reduced incidence of any VTE in neurosurgical patients[14], the quality of evidence is insufficient to make strong conclusions. At the same time, there is moderate-to-good quality evidence that IPC is comparable in efficacy to anticoagulants in this cohort17. The analysis did not reveal any significant difference in the effectiveness of IPC and GCS[8]. They may be suitable for patients who are at risk for bleeding or have contraindications to anticoagulation. However, the benefit of IPC devices for bedridden or patients or those with limited mobility is questionable, as they interfere with early mobilization. Compared with IPC, GCS are inexpensive, easy to use and can be worn continuously. IPC and GCS should be used as an adjunctive to other type of thromboprophylaxis.

More controlled trials are needed to study the effects of pharmacological and mechanical thromboprophylaxis used separately or in combination in hospitalized patients.

CONCLUSIONS

The prevention of pulmonary embolism (PE) is complex and continues to generate debate. This review of systematic reviews and meta-analyses from 2020 to 2023 highlights significant inconsistencies and uncertainties in the effectiveness of current prevention strategies. Both pharmacological and mechanical methods, as well as their combinations, have produced mixed results with varying levels of evidence and considerable methodological bias. Our review, based entirely on data from systematic reviews and meta-analyses, has theoretical novelty, especially for vascular surgery in post-Soviet countries.

The findings have particular relevance for healthcare systems in post-Soviet countries, where the theoretical novelty of this review could guide future research and clinical practices in vascular surgery. This study provides a crucial foundation for improving the understanding and effectiveness of PE prevention strategies, potentially leading to better patient outcomes worldwide.

Though, it is necessary to conduct a larger number of studies, such as randomized controlled trials, with minimizing the level of methodological bias on the mentioned set of means of preventing PE. This should be done in order to eliminate the controversial and ambiguous nature of the means of preventing PE in the research environment.

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