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SYSTEMATIC REVIEW

Utility of unfractionated sodium heparin in the prevention of disseminated intravascular coagulation

Utilidad de la heparina sódica no fraccionada en la prevención de la coagulación intravascular diseminada

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ABSTRACT

Introduction: disseminated intravascular coagulation (DIC) is a serious disease characterized by a generalized activation of blood coagulation, with sequelae ranging from thrombus formation to severe bleeding.
Objective: to analyze the fundamental alternatives for the management of DIC prevention related to the use of unfractionated heparin.
Method: data collection was carried out through a search in the digital databases PubMed, SciELO (Scientific Electronic Library Online) and Google Schoolar. The articles were downloaded from the aforementioned platforms, and the Zotero system was used to make the corresponding citations and pertinent references.
Results: according to the results achieved, the systematic review allowed to obtain a more detailed view of the studies arising from the data search, related to DIC and the use of unfractionated heparin in its prevention. The importance of research related to this drug was highlighted to improve the understanding and treatment of DIC with the aim of reducing its morbidity and mortality.
Conclusions: despite unfractionated heparin presenting significant anticoagulant effects in its clinical utility, mainly in emergency situations due to its rapid action, there are few studies available for a better understanding of the management and functionality of UFH against DIC.

Keywords: Unfractionated Heparin; Disseminated Intravascular Coagulation; Prevention; Anticoagulant.

RESUMEN

Introducción: la Coagulación Intravascular Diseminada (CID) es una enfermedad grave caracterizada por una activación generalizada de la coagulación sanguínea, con secuelas que van desde la formación de trombos hasta hemorragias graves.
Objetivo: analizar las alternativas fundamentales para el manejo de la prevención de la CID relacionada al uso de la heparina no fraccionada
Método: la recolección de datos se llevó a cabo mediante una búsqueda en las bases de datos digitales. PubMed, SciELO (Scientific Electronic Library Online) y Google Académico. Los artículos fueron descargados de las plataformas mencionadas, y se empleó el sistema Zotero para efectuar las correspondientes citas y referencias pertinentes.
Resultados: de acuerdo con los resultados alcanzados, la revisión sistemática permitió obtener una visión más detallada de los estudios surgidos de la búsqueda de datos, relacionados a la CID y la utilización de la heparina no fraccionada en su prevención. Se destacó la importancia de la investigación relacionada al dicho fármaco para mejorar la compresión y el tratamiento de la CID con el objetivo de reducir su morbilidad y mortalidad.

Conclusiones: a pesar de la heparina no fraccionada presentar efectos anticoagulantes significativos en su utilidad clínica, principalmente en situaciones de emergencia debido que posee una rápida actuación, hay una poca cantidad de estudios que están disponibles para un mejor entendimiento del manejo y de la funcionalidad de la HNF frente a la CID.

Palabras clave: Heparina no Fraccionada; Coagulación Intravascular Diseminada; Prevención; Anticoagulante.

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a severe complication characterized by an intense activation of the hemostatic system, leading to the formation of blood clots and the appearance of severe hemorrhages.[1,2] It is unrelated to a specific cause; it presents different origins ranging from serious infectious diseases to cancer or injuries.[3,4]

The disease results from exposure and release of the Tissue Factor (TF) by different cells into the blood, which triggers a series of events leading to thrombin formation, fibrinolysis stimulation, and inflammatory response activation.[5] Heparin is generally recognized as an essential tool to combat and prevent DIC; it is a natural substance formed by sulfated mucopolysaccharides and has anticoagulant properties.[6,7] The efficacy of unfractionated heparin (UFH) in improving clinical outcomes is a matter of debate as it has a more potent but less predictable action compared to other treatments used and is more indicated in emergencies.[8,9]

UFH and antithrombin III can inhibit several coagulation factors, including thrombin and factor Xa, preventing clot formation. Its anticoagulant effect is rapidly noted in laboratory experiments and living organisms and plays a fundamental role in its progression.[10] This systematic review explores the fundamentals of DIC and the use of unfractionated heparin in its prevention. The importance of research related to this drug to improve the compression and treatment of DIC to reduce its morbidity and mortality is highlighted.

DIC occurs as an excessive activation of the hemostatic mechanism and the inability of physiological inhibitors to neutralize coagulation. This process is initiated by releasing the Tissue Factor (TF) by monocytes, endothelial cells, and cancer cells. All that leads to a sequence of events involving thrombin formation, fibrinolysis promotion, and the activation of inflammatory response.[5] The relationship between inflammation and coagulation plays an essential role in developing DIC, where inflammatory cytokines such as IL1 and TNFα contribute to clot formation and neutrophils cause a reduction in microvascular blood flow.[11,12] In the vascular endothelium are the mechanisms of coagulation control, and where the interaction between coagulation and inflammation occurs, dysfunction of this organ plays a crucial role in the progression of DIC.[11]

Cell activation and the release of inflammatory cytokines generate an imbalance between the hemostatic system and clot dissolution, resulting in the consumption of coagulation factors and anticoagulant proteins such as protein C and antithrombin. Its pathophysiological mechanism has a complex interaction between coagulation activation, inflammatory response, and endothelial dysfunction, leading to a generalized coagulopathy with a high potential for morbidity.[13]

The diagnosis of DIC is based on clinical findings such as excessive bleeding, thromboembolism followed by laboratory tests such as hemostatic molecular markers abnormal coagulation test, in addition to other studies and scoring systems such as those established by the International Society of Thrombosis and Hemostasis/ Scientific and Standardization Subcommittee (ISTH/SSC), Japanese Ministry of Health and Welfare (JMHLW) and the Japanese Association for Acute Medicine (JAAM), these systems include international coagulation tests to stage disease severity and outcome.[5,13]

The CID score proposed by ISTH can help predict mortality in patients who have developed this disease. Coagulation tests, such as thromboelastography (TEG), can provide a comprehensive view of hemostatic function in critically ill patients. The diagnosis of DIC is an extensive analysis that combines clinical findings and laboratory results, using an international system of testing and certification to ensure proper identification and treatment.[11,12]

Heparin, a naturally occurring substance formed by sulfated mucopolysaccharides, has anticoagulant properties. Acting together with antithrombin III, it is able to inhibit several coagulation factors, including thrombin, preventing clot formation. Its anticoagulant effect is rapidly noted in laboratory experiments and living organisms. Although the digestive system cannot readily absorb it nor cross the placental barrier, it becomes part of plasma proteins, passes through metabolic processes in the liver, and is eliminated in the urine, with a biological half-life of 60 to 90 minutes.[9,10]

Heparin can modify its molecular weight and anticoagulant activity; its main action is produced by binding to antithrombin III, inhibiting thrombin and factor Xa. The interaction of heparin with platelets and endothelial cells can trigger side effects, such as bleeding and bone loss, even outside of its anticoagulant function.[7]

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The medical application of heparin as an anticoagulant prompted research on its impacts and characteristics. In addition to its antithrombotic action, non-coagulation properties, such as regulating adhesion molecules and releasing tissue factor pathway inhibitor (TFPI), have been discovered.[6]

Although its anticoagulant and non-anticoagulant functions contribute to its therapeutic efficacy, coagulation-promoting properties, such as stimulating inhibition of activated protein C, have also been observed. Heparin has various clinically relevant effects, but its procoagulant effects should be considered and monitored, especially in specific clinical scenarios.[8]

Therefore, this article aims to analyze the fundamental alternatives for the management of DIC prevention related to the use of unfractionated heparin.

METHOD

Data collection was carried out by searching digital databases: PubMed, SciELO (Scientific Electronic Library Online), and Google Academic, without language restrictions, using the following keywords: (unfractionated heparin + prevention of disseminated intravascular coagulation) yielded multiple results, multiple articles were obtained that were analyzed in-depth, of which 13 articles were selected for the final analysis, through a database filtering process.

Inclusion criteria: articles published in scientific journals between 2002 and 2023 - free full-text access; articles dealing with pathophysiological alterations for the development of DIC; articles covering the management of the different treatments for DIC; articles identifying the clinical criteria for diagnosis and better identification of DIC; articles dealing with the mechanism of action of unfractionated heparin sodium and its action against DIC.

Exclusion criteria: articles not dealing with DIC, articles on pregnant women and pediatric patients, and articles dealing with other drugs related to DIC.

With the results of this search, and after a careful selection based on the inclusion and exclusion criteria, titles and abstracts were read to ensure that they corresponded to the central question of this study (What is the available evidence on the use of unfractionated sodium heparin in the prevention of DIC?), followed by a phase of reading relevant publications and articles in terms of variables and clinical outcome measures of the different studies to identify possible similarities and differences between them. At the end of the process, 13 articles remained for the final analysis.

For the data search, it is necessary to use developed tools that ensure the extraction of relevant information, reduce the risk of transmission errors, and guarantee the accuracy of the verification and recording of the information. The purpose of this tool is to provide clear guidelines on the distribution of articles and authors, year, objectives, and design of the database, taking into account the limitations presented, which are the small number of studies that are available for a better understanding of the functionality of UFH versus DIC.

RESULTS

The treatment of DIC is very complex and must be adapted to the profile of each patient. This topic is paramount for healthcare professionals and those still in training. Despite the small number of studies available for the better understanding and management of FNH versus DIC, a combination of 13 articles were analyzed, where it was possible to find complete results, where they were organized and classified in each category, with links referring to issues that vary from year to year, in the title of the research and objectives of each study. Based on the articles analyzed, it was possible to create a table with the results referring to the systematic review of the topic addressed in this thesis.

Table 1. Results of the analysis of the articles

General Recommendations	Generally speaking, LMWH is preferred over UFH, and UFH is considered at therapeutic doses for thrombosis.
Efficacy of UFH	It presents a higher risk of bleeding compared to other treatments.
VTE prophylaxis	Thromboembolic prophylaxis with UFH is standard in DIC, especially in the prevention of DVT in patients without active bleeding.
Experimental Studies	There are studies suggesting that UFH has the necessary properties to inhibit coagulation, evidence of relevant clinical improvements is still lacking.
Use in Sepsis	The use of UFH does not show significant improvement in mortality in sepsis, but it is essential for thromboembolic prophylaxis.
Bleeding Risk	UFH is not recommended in cases of active bleeding, only as prophylaxis in high-risk patients without active bleeding.

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Table 2. Comparative studies between LMWH and UFH in patients with thromboembolic diseases

Characteristic	HBPM	HNF
Age of Patients	Average: 58 years old Range: 40-75 years	Average: 62 years old Range: 45- 80 years
Sex	55 % men, 45 % female	60 % men, 40 % women
Pre-existing Conditions	Deep Venous Thrombosis (DVT) Unstable Angina	Pulmonary thromboembolism (PTE) Myocardial Infarction (AMI)
Results	Reduced incidence of thrombocyte Penia Reduction in hemorrhagic complications	Better control of aPTT Reversibility with Protamine
Disadvantages	Need for adjustment for body weight	Requires frequent monitoring of aPTT (activated partial thromboplastin time).

DISCUSSION

The use of unfractionated heparin (UFH) as a treatment for patients with DIC was examined. In the early stage of DIC, UFH is often considered to control uncontrolled coagulation activation. However, findings from several studies indicate that continued evaluation is required to determine the most effective treatment. In retrospective cohort studies, UFH demonstrated that patients with DIC had different mortality rates. One high-quality study found that the UFH-treated group had a higher mortality rate than LMWH. In contrast, another lower-quality study found no significant difference in mortality between UFH-treated and untreated patients. These results suggest that the effectiveness of UFH may depend on the clinical setting and the quality of the study.[9]

The results of UFH compared with other anticoagulants were also mixed in randomized clinical trials (RCTs). In one study, UFH did not reduce the mortality rate compared with placebo but significantly reduced the duration of mechanical ventilation in patients with DIC and respiratory distress syndrome. In another study, activated protein C (APC) was more effective in this regard, but heparin showed positive effects in reducing the mortality rate. Recent studies have also observed that UFH may have additional anti-inflammatory effects, which could be advantageous in the early stages of DIC, especially considering the interaction between inflammation and coagulation in this state. In cases where inflammation is essential, such as sepsis, this anti-inflammatory effect of UFH could be an essential factor in the choice of therapy.[8]

The high heterogeneity in study populations and intervention/control groups is an essential limitation of the reviewed studies. This, together with the paucity of specific studies on UFH in DIC, makes it difficult to perform a robust meta-analysis and to generalize the findings. Therefore, more well-designed clinical trials are required to evaluate the efficacy of UFH in different underlying conditions and early stages of DIC.[13,14]

CONCLUSIONS

UFH remains an essential option for DIC, especially for prophylaxis in patients at high risk for thromboembolic events and without active bleeding. However, further research on its efficacy is still needed compared with other anticoagulants, such as LMWH and APC. Identification of patient subgroups that might benefit most from UFH, as well as optimization of doses and methods of administration, should be the focus of future studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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