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Research Article **Open Access Journal**

Therapeutic Potential of Heparin in Sepsis Per Gram Negative

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Abstract:

Background: Heparin is the oldest anticoagulant used in clinical medicine. Heparin has been studied for various applications and modifications. Gram-negative bacteria are among the most important public health problems in the world due to their high resistance to antibiotics.

Methodology: A narrative review was carried out through various databases from January 2012 to December 2021; the search and selection of articles was carried out in journals indexed in English. The following were used as keywords: Heparin, sepsis, Gram negative.

Results: Key factors in the development of sepsis include the release of pro-inflammatory mediators, diffuse endothelial injury, and procoagulant reactions, followed by organ dysfunction, taking into account that pro-inflammatory mediators activate coagulation. Heparin is a glycosaminoglycan with anticoagulant properties and anti-inflammatory effects.

Conclusions: This review offers updated information on the therapeutic role of heparin in patients who develop sepsis after infection with Gram-negative bacteria.

Keywords: Heparin, Sepsis, Gram negative.

Introduction

Heparin is the oldest anticoagulant used in clinical medicine. Paradoxically, heparin was discovered by Mclean in 1916 in an attempt to isolate a thromboplastic agent. (1) Heparin is a natural polysaccharide belonging to the family of glycosaminoglycans present ubiquitously in mast cells. Subsequent work finally led to its beginning in clinical use in 1935. Since then, heparin has been studied for various applications and modifications. (2)

Unfractionated heparin is an anticoagulant indicated both for the prevention and treatment of thrombotic events such as deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as atrial fibrillation (AF). (23)

It is also used to prevent excessive clotting during procedures such as heart surgery, cardiopulmonary bypass, or dialysis, including continuous renal replacement therapy. Heparin is also widely used in the hospital for many different

off-label indications. (3,4) When heparin toxicity occurs, protamine is recommended to reverse the anticoagulant effect of heparin. (4,5) Patients with severe or life-threatening bleeding or patients undergoing surgery may require protamine for reversal. (5,6) Heparin neutralization occurs when protamine binds to heparin by ionic properties. (7,8)

Gram-negative bacteria are among the most important public health problems in the world due to their high resistance to antibiotics. (9,10) These microorganisms are of great clinical importance in hospitals because they often require patients to be in the intensive care unit (ICU) and patients are at high risk of morbidity and mortality. Two large groups, Enterobacteriaceae and non-fermenters, are responsible for the majority of clinical isolates. (11, 12)

Since gram negatives are among the most important public health problems, sepsis represents a great challenge in medicine. Beginning as a systemic response to infection that can affect virtually any organ system. It was decided to carry out this work to identify other possible therapeutic approaches, such as heparin, in Gram-negative Sepsis.

Materials and Methods

A narrative review was carried out, in which the PubMed, Scielo and ScienceDirect databases, among others, were searched. The collection and selection of articles was carried out in journals indexed in English from the years 2012 to 2021. As keywords, the following terms were used in the databases according to the DeCS and MeSH methodology: Heparin; sepsis; Gram negative. In this review, 77 original and review publications related to the subject studied were identified, of which 20 articles met the specified inclusion requirements, such as articles that were in a range not less than the year 2012, that were articles of full text and to report on the therapeutic potential of heparin in gram-negative sepsis. As exclusion criteria, it was taken into account that the articles did not have sufficient information and that they did not present the full text at the time of review.

Results

Effects of Heparin in Sepsis

Key factors in the development of sepsis include the release of proinflammatory mediators, diffuse endothelial injury, and procoagulant reactions, followed by organ dysfunction. Mounting evidence indicates a broad interaction between inflammation and coagulation that may play a vital role in the pathophysiology of sepsis. (13)

Proinflammatory mediators activate coagulation, which promotes inflammatory activity in many ways. More commonly, the coagulation cascade interacts with the inflammatory pathway and induces activation of endothelial cells, which may express a procoagulant phenotype. Increased production of inflammatory mediators and leukocyte adhesion result in secondary dysfunction of internal organs. (13)

The coagulation cascade begins with tissue factor expression in circulating monocytes, tissue macrophages, and possibly endothelial cell subsets. (14)

Heparin is a glycosaminoglycan with anticoagulant properties and anti-inflammatory effects. It has been widely used in clinical practice for various indications, especially for the prevention and treatment of venous thromboembolism. (fifteen)

Coagulation is a complicated process that involves platelets, soluble proteins, and cellular components, such as monocytes and endothelial cells. and hemostasis is maintained by the balance between coagulation factors and coagulation inhibitors. The main plasma coagulation inhibitor is antithrombin, which targets activated coagulation factors, such as factors XIIa, XIa, Xa, IXa, VIIa, and thrombin. (14)

Heparin interacts with the coagulation system in multiple ways, but its interaction with antithrombin to inhibit the action of thrombin and factor Xa is unique. (16)

Heparin exerts an anticoagulant effect by binding to the lysine site on antithrombin, thereby inducing a non-reversible conformational change in the arginine-reactive site in such a way as to inhibit thrombin up to 1000-fold. Thrombin inhibition requires a heparin chain comprising at least 18 saccharide units. Therefore, it can occur with unfractionated heparin, but not with low molecular weight heparin. (17)

The heparin-antithrombin complex inactivates a number of coagulation enzymes, including thrombin, factors Xa, IXa, XIa, and XIIa. Among these, thrombin and FXa are the most critical and sensitive within the coagulation cascade. And

thrombin is approximately 10 times more sensitive to inhibition by the heparin-antithrombin complex than is FXa. In figure 1 we can see in more detail the mechanism of action of heparin. (16)

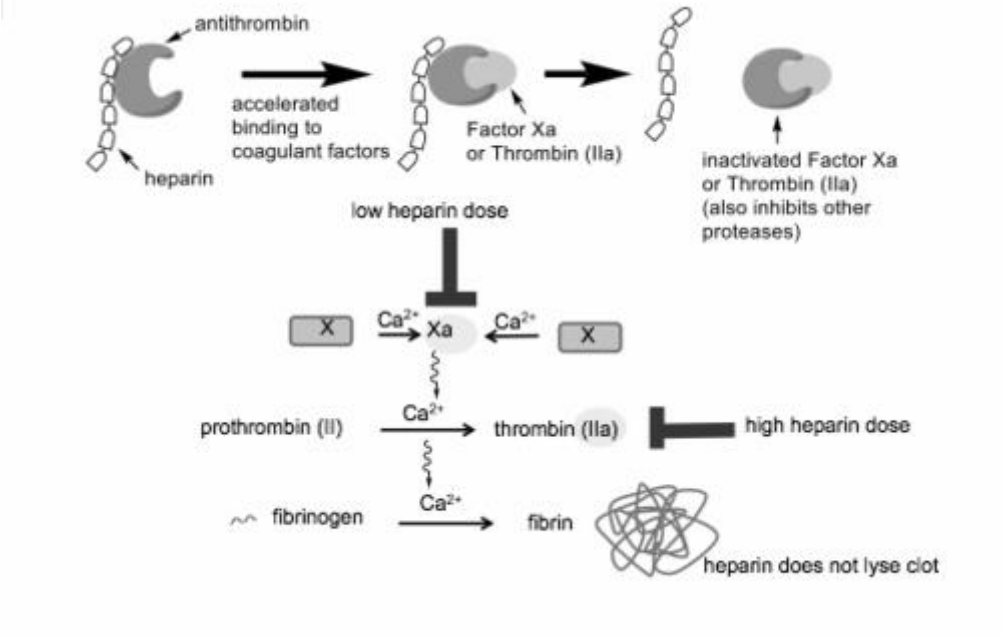

Figure 1. Heparin action mechanism: Heparin exerts its anticoagulant action by stimulating antithrombin III (ATIII) activity. This action of heparin is due to a unique pentasaccharide sequence with high affinity binding to ATIII. This high-affinity binding sequence is present in only one-third of heparin molecules. The interaction of heparin with ATIII produces a conformational change in ATIII, which accelerates its ability to inactivate the coagulation enzymes thrombin (Factor IIa), factor Xa, and factor IXa. Of these enzymes, thrombin is the most sensitive to inhibition by heparin/ATIII.

Heparin contributes to the treatment of sepsis in various ways, of which those exerted by anticoagulant and immunomodulation effects stand out, as evidenced in Table 1.

Table 1. Heparin and its effects

EFFECTS	FUNCTIONS
Anticoagulation	**B**inds to antithrombin
	Binds heparin cofactor II
	Inhibits thrombin-induced activation of FV and FVIII
	Promotes the release of TFPI
Immunomodulation	Inhibits inflammation and prevents mortality
	Inhibits lung inflammation by activating NF-κB
	Inhibits platelet activation
	Inhibits neutrophil recruitment
	Inhibits LPS-induced inflammatory mediators
	Inhibits angiogenesis
	Modulates pulmonary hypertension
	Inhibits pulmonary edema
	Inhibits the functions of neutrophils
	Reduces eosinophil migration

Activation of the coagulation cascade is involved in an effective host immune response against some Gram-negative bacteria. (14)

Certain types of bacteria, such as Salmonella enterica, are gram-negative, facultative intracellular organisms that cause hundreds of thousands of deaths each year, and the risk of death is markedly increased when the bacteria invade systemically. (19)

In most bacterial infection models using Gram-negative bacteria, thrombosis is detected within minutes to hours after infection. (twenty)

A variety of disorders (sepsis, systemic inflammatory conditions, trauma, malignancies) lead to activation of the coagulation system, and microvascular thrombosis is a frequent complication of critical illness. (18)

Therefore, here we can demonstrate the therapeutic potential that could be implemented in patients with gram negative infections. Since it has been shown that gram negative infection induces coagulopathies, causing high mortality and morbidity. (17)

The use of heparin in patients with gram-negative sepsis could significantly reduce hospital stay and ICU admissions, by inhibiting the coagulopathies that these patients present. (16, 20)

Discussion

The results obtained in this study support a beneficial effect of heparin as a therapeutic effect by reducing mortality and morbidity in patients with systemic inflammation causing coagulopathies secondary to Gram-negative sepsis.

This work is supported by different studies, such as the one carried out by Zarychanski et al, in which randomized trials were carried out investigating unfractionated or low molecular weight heparin administered to patients with sepsis, severe sepsis or septic shock associated with infection, in which they conclude that heparin in patients with infection-associated sepsis may be associated with decreased mortality. (twenty). As is well known, sepsis continues to be a cause of high mortality, and there are no proven treatment strategies for the routine management of patients with sepsis. Furthermore, inflammation and coagulation contribute to the basic pathophysiology of sepsis. Therefore, drugs that attenuate these effects are needed. This question was raised in the work carried out by Xu-Li et al, in which heparin is proposed as an agent that attenuates the activation of both inflammation and coagulation, improving the present sepsis, and also has immunomodulation properties . (12)

A strength of the current study is the implemented methodology, regarding the literature search, and steps in the selection of relevant articles, quality assessment and data extraction. However, this study has several limitations, which should be taken into account before reaching a conclusion, among which is the lack of evidence from the analysis of clinical trials to accurately determine the efficacy of heparin in patients with gram-negative sepsis.

Conclusion

Key factors in the development of sepsis include the release of proinflammatory mediators, diffuse endothelial injury, and procoagulant reactions, followed by organ dysfunction, considering that proinflammatory mediators activate coagulation. Heparin is a glycosaminoglycan with anticoagulant properties and anti-inflammatory effects.

Heparin interacts with the coagulation system in multiple ways, but its interaction with antithrombin to inhibit the action of thrombin and factor Xa is unique. The heparin-antithrombin complex inactivates a number of coagulation enzymes, including thrombin, factors Xa, IXa, XIa and XIIa, exerting anticoagulant and immunomodulatory effects.

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