Heparin Resistance in surgical patients: Could individualized prophylaxis through recognition of high and low responders to antithrombotic treatment represent an option to optimal antithrombotic strategy in the future?

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Abstract:

Background: Heparin Resistance (HR) represents a considerable risk factor for perioperative and postoperative complications in surgical patients. These complications are expressed with venous and/or arterial thrombotic events which compromise the patient's outcome after surgery. HR commonly occurs in patients with coronary disease undergoing cardio-pulmonary by-pass, cancer patients, as well as in patients suffering from AT-III deficiency, or type II H.I.T (Heparin induced thrombocytopenia). Nevertheless, HR occurred also in healthy volunteers and in Oncologic Surgery, and according to our findings, also in Major Orthopedic Surgery and in Vascular Surgery. The purpose of the current review was to focus on the considerable percentage of HR among surgical patients.

Material and Methods: The literature search included the following key words: HR, venous thromboembolism (VTE) and surgical, cardiovascular, ongological, orthopaedic and vascular patients and included reports published between 1990 and 2016. Only articles listed in Pubmed and written in English were included. The aforementioned criteria provided a total of 1948 papers. After the exclusion of papers regarding patients with thrombophilia, HIT and antithrombin III deficiency, the total sum of articles relevant and important to the subject was 43, which were analyzed in detail in the current article.

Results: In 2 studies the relation between low molecular weight heparin (LMWH) and HR in healthy volunteers was investigated. Both confirm that presence of HR in healthy volunteers is not rare. Four papers from the included studies refer to the physiologic mechanism through which HR is expressed in cancer patients. Seven studies refer to the Major orthopedic surgery in relation to the HR. The presence of HR in oncologic surgery was commented only in one paper. In coronary patient we found 14 references related to specific theme. Among them 2 studies examined the efficiency of LMWH's antithrombotic activity. In 23,2% of papers, HR in patients undergoing coronary bypass graft surgery treated with UFH, was investigated. Only two papers investigate HR in patients receiving coronary bypass who were treated preoperatively with LMWH and perioperatively with UFH. Two papers were guidelines to prevent VTE, in high-risk surgical patients and one investigated the antithrombotic properties of LMWH in plasma. Finally, three studies are related to the properties of the Thrombogram-Thrombinoscope (TG assay) laboratory method in clot cascade.

Conclusion: Personalized antithrombotic treatment using the method of Calibrated Thrombin Generation Assay may represent a solution to optimal treatment in future antithrombotic strategy.

Keywords: Heparin Resistance, UFH, LMWH, TG, VTE, Orthopedic Surgery, Vascular Surgery, Oncologic Surgery, Healthy Volunteers, Optimal Antithrombotic Strategy.

INTRODUCTION

In patients suffering from Venous Thromboembolism (VTE), Heparin Resistance (HR) is defined as a pathological situation in which, patients require unusually high doses of heparin to achieve the desirable antithrombotic response and therapeutic aPTT levels. In these cases, the daily heparin requirement may reach and overcome the amount of 35.000 anti-Xa IU/d.[1] HR occurs in 25% of patients with VTE.[2] Gionis et al. using the method of Thrombin Generation (TG) assay, defined Biological Resistance to Low Molecular Weight Heparin (LMWH), as any abnormal alteration of TG specific biomarkers, in surgical patients receiving thromboprophylaxis with LMWH, on the 8th postoperative day -were maximum anti-Xa effect of LMWH is expected-, compared to the same TG biomarkers on the day before surgery where no anticoagulants were somministrated.[3,4]

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Pathophysiologic mechanisms and mode of action of HR

The proposed mode of action of HR includes various mechanisms for different types of patients. These mechanisms are based on Antithrombin (AT) Deficiency, increased heparin

clearance, high amounts of heparin-binding proteins and high levels of Factor VIII and/or fibrinogen.[1] The risk factors for HR are classified in AT- mediated and non AT- mediated. In detail, they are listed in table 1.

Type	Risk factors
AT- mediated HR	• reduced AT synthesis congenital or acquired • accelerated AT clearance because of nephropathy • consumption due to preoperative use (>24 hrs) of UFH or LMWH • in case of endocarditis • in cardiopulmonary by-pass • ventricular assist device • intra-aortic balloon pump
Non AT- mediated	• higher than 300.000/ml preoperative platelet counts • plasma albumin concentration <35 gr/dl • drugs (concomitant infusion of nitroglycerin

Table 1. Risk factors classification for HR

Biological heparin resistance (HR) has been found to commonly occur in cancer patients and to a lesser extent in patients with anti-thrombin deficiency, or type II heparin induced thrombocytopenia.[5,6] The mode of action in which HR is expressed implicates Unfractioned Heparin (UFH),[6] as well as Low Molecular Weight Heparin (LMWH).[5] In oncologic patients HR is not rare, since tumor cells contribute to an overexpression of Heparanase (an endo-D-glucuronidase) that cleaves heparin sulfate, resulting in a marked suppression of the anticoagulant activity of UFH and LMWH.[5] Beyond oncologic patients, HR often occurs in patients with Antihrombin III deficiency, or type II H.I.T. In fact, UFH's main effect consist to the activation of Antithrombin (AT) and consequently to the inactivation of both Factor IIa (Thrombin) and Factor Xa.[6] AT-dependent HR mainly occurs in congenital AT deficiency, asparaginase therapy, disseminated intravascular coagulation (D.I.C.), and administration of high doses of UFH during extracorporeal circulation, since an activated clotting time (ACT) major to 400 sec is necessary.[7] Type II H.I.T. is not a true HR, but an autoimmune complication, requiring heparin discontinuation and the use of an alternative anticoagulant agent.[6] HR expressed as inability to achieve therapeutic anticoagulation, has been described in a high percentage (22%) of patients undergoing coronary surgery treated with UFH, or UFH and LMWH, often with catastrophic complications.[8-10] Regarding the mode of action of LMWHs, these are commonly used as antithrombotic agents in the majority of surgical diseases. These are pleiotropic anticoagulant drugs which exert their antithrombotic activity by inhibiting thrombin generation (TG) via the Antihrombin dependent inhibition of serine proteases (factor Xa and to a lesser extent by inhibiting factor IIa, factor IXa).[11-14] In addition, LMWHs inhibit factor's VIIa generation and activity and induce Tissue Factor Pathway Inhibitor (TFPI) release that contributes to their antithrombotic effect.[15-17] On the other hand, the longer glycosaminoglycan chains of LMWH bind non-specifically to plasma proteins, and part of its antithrombotic activity is neutralized by platelet factor 4 (PF4) released from activated platelets.[18] Activation of platelets, leukocytes and endothelium cells is enhanced during the perioperative period, inducing hypercoagulable state.[19]

Controversies about laboratory methods of measuring the antithrombotic efficacy

Measurement of anti-Xa plasma activity is still regarded as the only test for biological monitoring of LMWH treatment. Nevertheless, it has been shown that for patients receiving thromboprophylaxis with LMWH, the concentration of anti-Xa activity in plasma is not well correlated with the clinical outcome, although this has not been the case for patients with acute coronary syndromes treated with LMWH.[20-22] Measurement of anti-Xa activity in plasma represents only one aspect of LMWHs' activity, since they interfere into several steps of blood coagulation. Dosage of anti-Xa activity is performed in platelet poor plasma. LMWHs' antithrombotic activity is partially inhibited by PF4.[18,22] Global coagulation assays sensitive to LMWHs could probably better reflect their antithrombotic efficacy.[23] The analysis of the influence of LMWH treatment on the distinct phases of blood coagulation in clinical settings where the thrombotic risk is increased could be a breakthrough step towards the development of a new individualised option regarding future strategies in thromboprophylaxis.

Clinical aspects of HR and effects on various types of patients

In Oncologic Surgery, Papageorgiou et al.,[24] have recently demonstrated the presence of resistance to thromboprophylaxis with LMWH administered postoperatively in patients undergoing lobectomy for lung adenocarcinoma. In Major Orthopaedic Surgery (MOS), Elective Total Hip Replacement (THR) and Total Knee Replacement (TKR) are the commonest interventions associated with a high risk of venous thromboembolism (VTE) which persists for several weeks after the surgery.[25] Post-Operative thromboprophylaxis consists to a routine administration of a fixed dose of Low Molecular Weight Heparins (LMWHs), fondaparinux, orally active direct inhibitor of factor Xa, or thrombin inhibitors, and is strongly recommended for these patients.[25,26] LMWHs are the commonest anti-thrombotic drugs administered during the post-surgery period and present predictable pharmacokinetics allowing effective thromboprophylaxis with a single daily subcutaneous injection.[27] Although LMWHs represent a substantial improvement in the antithrombotic strategy, about 10% to 20% of patients undergoing MOS, who receive the recommended prophylaxis with LMWH may still present asymptomatic VTE.[28-30] HR is not a rare phenomenon in patients undergoing THR or TKR, and could be part of the explanation for the high percentages of VTE during the post-operative period.[3,4] In Vascular Surgery, HR is also present in considerable percentage of patients despite intraoperative administration of UFH before arterial clamping, as well as, postoperatively with LMWH's somministration.[4] In Cardiac Surgery, HR is reported in up to 22% of patients undergoing cardiopulmonary bypass.[33-35] It is usually defined as failure to reach a certain Activated Clotting Time (ACT<400 sec) value after a certain bolus administration of heparin (full dose heparinization for open heart surgery); however, there are varying proposals as to what those given

values are.[33-38] Another approach was introduced by Ranucci et al, who proposed the use of a Heparin Sensitivity Index (HSI), with values less than 1.3 indicating heparin resistance.[39] There is general agreement that heparin resistance is more common in patients receiving UFH preoperatively,[35,36,40,41] however, this may be extended also to patients treated with LMWH.[9,10] It is not clear whether heparin resistance is of significant clinical relevance. Nicholson et al. proved that despite the ACT being frequently less than 400 seconds, no coagulation was seen in their group of heparin-pretreated patients, and suggested that a standard heparin dose should always be safe and sufficient.[42] The impact of HR on the outcome of cardiac surgical patients is unclear. The only study that addressed this issue was published by the Ranucci group in the European Journal of Anesthesiology - the authors found that heparin resistance (and heparin pretreatment) was associated with increased incidence of postoperative fatal myocardial infarction.[39]

Discrepancy of antithrombotic efficiency in healthy volunteers

It is quite surprising that HR also occur in healthy volunteers.[32] Al Dieri et al., examined healthy volunteers receiving subcutaneously a single dose of LMWH and reported that in about 20% of the samples, collected within 24 hours after the injection, the inhibition of thrombin generation could not be predicted by the concentration of the anti-Xa activity in plasma, or by the variations of the body weight. The Coefficient of Variation (CV) regarding the anti-Xa and anti-IIa activity is 50% for UFH and 22-37% LMWHs. Fixed dosage of LMWH caused under-dosage of anticoagulation in 10-13% of healthy volunteers, and over-dosage in 5-11%. High or low response is an individual property independent of the type of heparin injected and only partially explained by variation of body weight.[32] The perspective of identifying high and low responders in antithrombotic treatment can avoid patient's exposition in increased risk of thrombotic events during prophylaxis period; Calibrated Thrombin Generation (TG) Assay, is a laboratory method that allows the identification of surgical patients with poor response to anticoagulants, and could consist to a breakthrough step in order to achieve optimal antithrombotic treatment for these patents, in future daily clinical practice.[3,4,11,13,27] The use of this method, in orthopedic, vascular and oncologic patients revealed high percentages of HR, a fact that raises concerns about the optimal thromboprophylaxis in surgical patients, and proves that a considerable number of these clinical categories, may be exposed to an increased risk of venous and/or arterial thrombotic events during the perioperative and postoperative period even though prophylaxis with LMWH is administered.[3,4,24] Thrombin Generation (TG) parameters allow the analysis of the initiation, amplification and inhibition phase of Thrombinogenesis, as well as, the integral amount of generated thrombin.[43] The use of a standardized assay allows the evaluation of the entire blood coagulation process and the global antithrombotic effect of LMWHs, in any desirable moment of the perioperative or the postoperative period of any single patient. This may have a major contribution regarding the optimal antithrombotic treatment in surgical patients. TG parameters are: 1. Lag-time, which describes the initiation phase of TG, 2. Peak concentration of Generated Thrombin, 3. Time necessary to Peak (ttPeak), 4. Endogenous Thrombin Potential (ETP), that reflects the total amount of thrombin in it's active form in plasma, and finally, 5. Mean Rate Index (MRI=Peak/ttPeak-Lag-time) which reflects the velocity of the propagation phase of TG. Biological HR to LMWH could be defined using this method as any variation of TG (increase in Peak, ETP & MRI, or decrease in Lag-time & ttPeak) on the 8th postoperative day, when the maximum anti-Xa effect of LMWH is expected, compared to TG on the day before surgery.[3,4] ETP and MRI are the most important biomarkers in order to identify the patients with low response to LMWH's treatment. TG Assay is a method that could easily be applicated in any laboratory.[3,4]

Review of the literature

Aiming to focus on the considerable percentage of Heparin Resistance to surgical patients despite receiving fixed-dose thromboprophylaxis according to current guidelines and to introduce the concept of individualized thromboprophylaxis as a perspective in future antithrombotic strategy we preformed a review of the literature.

The methodology or literature research followed the plan described subsequently. The key words used included: i) Heparine resistance (HR), ii) HR, VTE and surgical patients, iii) HR and cardiovascular patients, iv) HR and orthopedic patients, v) HR and vascular patients. The time period selected included article published between 1990 and 2016. Only articles listed in Pubmed and written in English were included. The inclusion and exclusion criteria are described in table 2.

	Inclusion criteria	Exclusion criteria
1	Heparine resistance	CRF
2	Thrombotic events in adults	COPD
3	Surgical patients	Any thrombophilia
2	Any study related to the criteria 1,2,3	Pregnancy

Table 2. Suitability criteria of the studies

The aforementioned criteria provided a total of 1948 papers. Among them six papers were related to "HR, VTE and surgical patients", 127 papers were related to "HR and cardiovascular patients", five papers to "HR and orthopedic patients", and 179 papers were related to "HR and vascular patients". After the exclusion of papers regarding patients with thrombophilia, HIT (Heparin induced thrombocytopenia) and antithrombin III deficiency, the total sum of articles relevant and important to the subject fell to 43, which were analyzed

in detail in the current article.

Among them: four papers investigate the physiologic mechanism through which HR is expressed in cancer patients treated with UFH or LMWH,[5] in patients treated with UFH,[6] and in patients with AT-III deficiency.[7,8] Nine papers study the mode of action and the antithrombotic properties of UFH and LMWH in laboratory, as well as in VTE patients.[2,11-18] One paper investigates the pathophysiology and the alterations of coagulability in patients undergoing MOS.[19] One paper investigates the relationship between antithrombotic activity of LMWH and the incidence of complications in patients underwent MOS[20]. Two papers investigate the efficiency of LMWH's antithrombotic activity in patients with acute coronary syndrome.[21,22] Two papers investigate the effect of LMWH in the clot cascade of healthy volunteers and the presence of HR also in healthy volunteers.[23,31] One paper studies the efficiency of LMWH's and the presence of HR in oncologic surgery.[24] Two papers regard guidelines to prevent Venous Thromboembolism (VTE), in high-risk surgical patients.[25,26] One paper investigates the antithrombotic properties of LMWH in plasma.[27] Three papers study the differences and the efficacy of antithrombotic properties between LMWH and Direct Thrombin Inhibitors (DTIs) in patients undergoing MOS.[28-31] One paper investigates the presence of HR using TG assay in patients underwent MOS, and treated with LMWH.[3] One paper investigates the presence of HR using TG assay in patients underwent MOS and Vascular Surgery and treated with LMWH, with/or without additional antiplatelet drugs.[4] In 10 papers the investigation refers HR in patients undergoing coronary bypass graft surgery, treated with UFH.[32,34-42] Two papers investigate HR in patients underwent coronary bypass graft surgery treated preoperatively with LMWH and peri-postoperatively with UFH.[9,10] Three papers study the properties of the Thrombogram-Thrombinoscope (TG assay) laboratory method in clot cascade.[14,27,43]

RESULTS

From 1990 to 2016 43 papers were reviewed. In 2 studies the relation of LMWH and HR in healthy volunteers was investigated. Both confirm the presence of HR in healthy volunteers which occurs in considerable frequency. Four papers (9,3%) from the included studies refer to the physiologic mechanism through which HR is expressed in cancer patients. In nine studies (20,9%) the mode of action and the antithrombotic properties of UFH and LMWH was examined. In two studies the alterations of coagulability in MOS patients were examined in relation to HR. Another three papers (6,9%) study the differences and the efficacy of antithrombotic properties between LMWH and Direct Thrombin Inhibitors (DTIs) in patients undergoing MOS. The presence of HR using TG assay in patients underwent MOS were examined in two further studies (4,6%).

The presence of HR in oncologic surgery was commented only in one paper (2,3%). In coronary patient we found 14 references (32,5%) related to the specific theme. Among them 4,6 % refers to the efficiency of LMWH's antithrombotic activity. In 23,2% of papers investigate HR in patients underwent coronary bypass graft surgery treated with UFH. Only two papers (4,6%) investigate HR in patients underwent coronary bypass treated preoperatively with LMWH and perioperatively with UFH. Two papers (4,6%) regard guidelines to prevent VTE, in high-risk surgical patients and one (2,3%) investigates the antithrombotic properties of LMWH in plasma. Finally three studies (7%) are related to the properties of the Thrombogram-Thrombinoscope (TG assay) laboratory method in clot cascade.

DISCUSSION

HR is defined as a phenomenon expressed with low responsiveness to anticoagulant treatment with UFH or LMWH. The implications of the main findings reported in literature about HR, may provide some perspections regarding future antithrombotic strategy.[1-4]

HR is documented in healthy volunteers who received LMWHs (up to 13%), leading to the conclusion that optimized individual dosage of LMWH is possible through recognition of high and low responders, which requires one measurement of the LMWH concentration or, preferably the LMWH's anticoagulant effect on the ETP, at least 2-5 hous after the first injection of the drug.[31]

In Cardiac surgery although HR is a well-known phenomenon in patients treated with UFH, this is not the case for the LMWHs. Even more, coronary patients treated with LMWH (enoxaparin) during the preoperative period, needed more UFH to maintain an ACT above 400 sec perioperatively, and had higher heparin concentrations and lower AT values compared with control patients. Patients treated preoperatively with LMWH had also higher neutrophil-activating peptide-2 concentrations. In other words, these patients treated with enoxaparin before cardiac surgery showed signs of HR intraoperatively and also had increased perioperative platelet activation.[10] In cardiac surgery, the use of preoperative LMWH remains a significant predictor of reduced intraoperative heparin responsiveness.[9]

In Oncologic surgery it has been found that, in patients with lung adenocarcinoma who underwent surgery and were treated with LMWH after surgery, 50% of the thrombin generated samples submitted to thrombin generation assessment (TG assay) collected postoperatively, an increase of TG occurred despite the presence of the expected anti-Xa activity in plasma. Additionally, on the 7-8th postoperative days (were maximum antithrombotic activity of the LMWH is expected), 3 out of 15 patients showed a significant increase of TG, leading to the conclusion that the response to enoxaparin is not predicted by the anti-Xa activity in plasma. Furthermore, TG is a laboratory method that allows to identify patients with residual plasma hypercoagulability.[24]

In Orthopedic surgery patients who underwent MOS, (Total Hip Replacement and Total Knee Replacement), treated postoperatively with LMWH (enoxaparin) according to ACCP guidelines, the study of thrombinogenesis using the method of TG assay, revealed considerable percentages of HR in both categories of orthopedic patients in the 8th postoperative day (were maximum antithrombotic effect of enoxaparin is ex-

pected).[3]

In Vascular surgery patients who underwent femoro-popliteal by-pass grafting and treated postoperatively with LMWH (enoxaparin), TG assay revealed considerable percentages of HR among the patients, in the 8th postoperative day, through increased TG (increased ETP & MRI) on this certain day that maximum antithrombotic effect is expected, when compared with TG preoperatively, were no LMWH was administered.[4]

CONCLUSIONS

It is clear that in the every-day clinical practice, a significant percentage of surgical patients considered as high-risk for venous or arterial thrombotic events, does not receive proper antithrombotic treatment, despite the fact that they receive thromboprophylaxis according to current guidelines, because of HR. This exposes them in possible and severe perioperative and/or postoperative complications. Identification of patients with low responsiveness to anticoagulant treatment due to HR, is quite important in order to achieve optimal antithrombotic prophylaxis for these patients. TG assay is a method that could directly identify every single patient with poor response to anticoagulant drugs. This could be a breakthrough step to future antithrombotic strategy. Further studies need to be done, in order to achieve optimal antithrombotic treatment and diminish hazardous perioperative and/or postoperative thrombotic events.

Conflict of interest: None

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