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Clinical Utilization of Non-Anticoagulant - A Review

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ABSTRACT

Heparin is used as anticoagulant for long period and also other activities both experimentally and clinically. The heparin is prepared by many methods namely enzymatic hydrolysis, chemical hydrolysis by removing the antithrombin binding sites or inactivating functional groups or units of this sequence. In non-anticoagulant treatments the therapeutic spectrum helps to the structural variations to treat different diseases. Sulfated non-anticoagulant heparins (S-NACHs) might be preferred for potential clinical use in cancer patients without affecting hemostasis. Among still some of the drugs or its derivatives are undergoing the clinical trials for various non-anticoagulant diseases. This review analyses the effects of this group of drugs on non-anticoagulant heparin, acute pulmonary embolism, oral pulmonary embolism, Non anticoagulant in cancer, Antitumor activities of LMWHs, dermatology, Effects of non-anticoagulant on Fractures such as bone metabolism, bone mineral density, Anti-inflammatory, asthma, Malaria Parasites, Anti-Human Immunodeficiency Virus, Non-anticoagulant activities of LMWHs with their mechanism, Non-anticoagulant pharmacological activities in clinical trials are discussed in this review.

Key words: Non-anticoagulant, Cancer, Anti-tumor, Asthma, Clinical trials, Fracture.

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INTRODUCTION

Low molecular weight heparins (LMWHs) and heparin normally used in the treatment and prevention of thrombosis disorder.[1] The heparin is well known for its anticoagulant activity apart from last ten years its witnessed for treat in non-anticoagulant i.e. in outside of thrombosis disorder disease.[2] The underlying mechanism of heparin are used in variety of non-anticoagulant treatment especially in anti-inflammation, cancer, osteoporosis etc.[3] The novel heparin based drugs produce an development for the opportunities various range to treat the disease and the pleiotropic the main disadvantage of heparin for treatment of various non-anticoagulant therapy.[4] The redundant activities of non-specific target the dilute may contribute to side effects.[5] The LMW Heparin which has molecular weight between 2000 to 8000 Da and produced by enzymatic or chemical analysis have shorter length when compared to unfractioned heparin (14000Da) and non-specific induced the sequences the activities have been removed during depolymerization process. So that it exhibits more potent activity than unfractionated heparin. LMWH side effects is less like fewer bleeding and heparin induced thrombocytopenia.

Moreover, LMW Heparin have more predictable pharmacokinetics, bioavailability and have longer half-life than heparin.[6] LMW Heparin has wider range of use in non-anticoagulant and also reduce the problem for use of normal heparin. So, in case of clinical studies it shows the various use of non-anticoagulant are estimated like anti-inflammatory, anti-metastatic and anti-fibrotic[7] activities. The structure-activity relationships (SAR) faced in non-anticoagulant problem for attributed development of drugs to undefined.

The anticoagulant activity heparin has pentasacchride and this was attached to antithrombin III (AT-III) and inhibit the factor Xa in coagulation cascades. The specific non-anticoagulant activity is depending on sequences of the heparin. Both non-anticoagulant and anticoagulant of selectivity is existing in the structure activity relationship. Structure cannot be simplified in three-dimensional architecture and also by primary composition sequence and substitution patterns. This binding directly on heparin protein interaction was not simply dependent on zonal regulation of the signaling network.[8] so the heparin involved in the complex protein network coupled with complexity of tools is difficulty to analysis to define the SAR.[9]

NON-ANTICOAGULANT HEPARINS

The unfractionated heparin is removed by its chain containing the sequence 4 for obtaining the non-anticoagulant heparin. This can be achieved by applying the precipitation or affinity chromatography complexation in anti-thrombin. For process 4 inhibited by which is essential for the high affinity of anti-thrombin through one or more groups of residual modification. By this residue the N-desulfation is removed from $N\text{-}SO_3$ groups as internal residues which involve in removal of dramatic drop sequence 4 for sulfa Mino group in anticoagulant activity. This also achieved by 2-O-desulfation i.e., Sulfate group removal in $IdoA_2SO_3$ residues in which the anti-thrombin has more affinity in this group in the marginal essential in sequence 4. So, 2-O-desulfation is marker active site of AT in internal residues and it loses essential 3-O-sulfate group. The anticoagulant activity from heparin is still modification decreased by GlcA residues of sequence 4. The bond between cleavages has the two hydroxyl groups and carboxyl group is reduced and the heparin activity is decreased. The glycol-split (gs) heparin is a reaction are most performed by period ate oxidation in quantitatively of all non-sulfated ironic acid residues in heparin.

This will not involve in major sequence 1 to ascribed the UH and LMWH in anti-thrombin mediated activities. The oxyheparin are reduced by oxidation of periodate heparin in non-sulfated ironic acid units (mostly GlcA but also IdoA) are designed and also reduce by stabilizing (forming CH 2OH groups) to the primary oxidation product (a polydialehyde). The

newly generated non-sulfated IdoA residues are obtained by controlled 2-O-desulfation of heparins and periodate oxidation/reduction of both the pre-existing of wide class of glycol-split heparin species.[10] The different structure of non-anticoagulant are listed with parent heparin like reduced oxyheparin, N-acetyl heparin and N-acetylated reduced oxyheparin the non-AT-mediated mechanism containing devoid of fractions chains of AT binding still has the anticoagulant properties. Desulfation involved in removal of sulfation groups which is located outside of the sequence and at has inhibition of thrombin and release the tissue factor pathway inhibitor (TFPI) in vascular tissues of heparin cofactor II (HC2). By means of pentasaccharide the factor inhibit Xa can be achieved efficiently by the sequence which is specifically provided the specific structure 4 AT binding site, the inhibition of thrombin should have five prolonged disaccharide units. Like the molecule dependent of heparin require the minimum chain length for expressing the activities in the AT- mediated and also by the anticoagulant HC2 induced by properties mediated in release of TFPI molecular weight.[11]

Anticoagulant treatment for acute pulmonary embolism

Due to right ventricular hemodynamic overload in the patients is challenging in the outcome and clinical presentation in the management of acute pulmonary embolism, due to vasoconstriction of neuro humor ally embolic obstruction of mechanically is overloaded by right ventricular. The pathophysiology of acute embolism has high risk in patient and low adverse effects, the risk is according to severity of embolism and the non-anticoagulant heparin is the main treatments for the above cases. So, in order to confirm the new direct oral non-anticoagulant compared with the five randomized clinical trials which include >11000 patient with pulmonary embolism. The patients with high risk of respiratory disorders (those with hemodynamics compromise) are not used in this study In this study direct oral non-anticoagulant have been showed as effective and safe for the embolism patients without hemodynamics compromise which are used in the study and its decided that this agent are correct measure treatment for intermediate high risk acute pulmonary embolism. Regardless of any risk stratification remains undefined. There are three clinical phases comprised for the treatment namely initial, long-term, extended treatments.[12] The main aim is to reduce the mortality, to identified in initial stage (first 5-10 days) and to reduce the late recurrence of long-term (mostly 3-6 months) and finally to reduce the late recurrences phase (beyond the first 3–6 months). With no treatment when compare to the treatment of two week it reduces ~70% of the mortality.[13] In recurrent symptomatic venous thromboembolism decrease statistically as non-significant and also weight adjusted treatment with LMWH in pulmonary embolism (1.4% versus 2.4%; OR 0.63, 95% CI 0.33–1.18) and major bleeding (1.4% versus 2.3%; OR 0.67, 95% CI 0.36–1.27) in comparison to APTT adjusted heparin.[14] Mortality cause difference (1.4% versus 1.2%; OR 1.20, 95% CI 0.59–2.45) between the two treatment strategies. Fondaparinux is an anticoagulant drug which have the anti-factor Xa activity and also a pentasaccharides, the dose is once daily by subcutaneously have effectively treated for pulmonary embolism[15] Idraparinux, given as SC once in a week it is Xa inhibitor for long acting and it is compared with heparin and by Vitamin K antagonists. It is used in clinical trials with 2215 patients as a randomized, with trial such as open and non-inferiority pulmonary embolism.[16] Idraparinux efficacy of the drug was not meet it requirements in non-inferiority requirement as a recurrence was 3.4 and 1.6 %. In conventional treatment group was OR 2.14, 95% CI 1.21–3.78. at end of 180 days studies it was observed the high risk of recurrence with treatment of idraparinux it was due to potential related under acute phase in the anticoagulation Due to above trial there a special attention for the non-anticoagulation in acute phase in the development of new treatment in the pulmonary embolism or with pre-treatment with heparin in acute phase. Pulmonary reperfusion with thrombolytic therapy given as a top priority of the disease as by lung scintigraphy and pulmonary angiography.

In hemodynamically with meta-analysis of studies of unstable patients shows reduced death comparison with pulmonary embolism in heparin as 50% alone (9.4% versus 19.0%; OR 0.45, 95% CI 0.22–0.92; number needed to treat, 10).[17] When compared with heparin the meta-analysis thrombolytic therapy reduces the mortality in the recent studies (OR 0.59, 95% CI 0.36–0.96).[18] As per statistically it is not significant in the not included in studies case of severe pulmonary embolism (OR 0.64, 95% CI 0.35–1.17). In first treatment after to all patients needed pulmonary embolism to stabilize the results which is obtained from 3-month treatment after the acute treatment.[19] In case of efficacy the drug of choice for the treatment is antagonism of Vitamin K by oral administration. In the treatment with cancer associated pulmonary embolism long-term treatment with LMWH should be preferred antagonism of Vitamin K.

Direct oral anticoagulants for acute pulmonary embolism

In the treatment of venous thromboembolism, a new oral anticoagulant was compared with currently used anticoagulant (warfarin). The patients with anticoagulant and hemodynamics therapy are not included in these studies. EINSTEIN-PE used in pulmonary embolism and it is only trial for the patients with diseases.

In this treatment the rivaroxaban was compared with conventional anticoagulant treatment. This treatment carried for 3,6 or 12 months as follow up by the direction of physician.[20] The 4832 patients were randomized as open label noninferiority trial. Without heparin pre-treatment the drug Rivaroxaban with 15mg of dose given 3 weeks twice daily and 20 mg is given once daily. The evidence of drug of rivaroxaban was obtained from the clinical trial of phase II in acute deep vein thrombosis.[21] In conventional therapy of Rivaroxaban the 2.1% and 1.8% occurred in thromboembolism patients respectively (hazard ratio 1.12, 95% CI 0.75–1.68; non-inferiority p=0.003). The non-major bleeding occur in the primary safety outcomes of major was 10.3% and 11.4% with rivaroxaban or conventional therapy patients' group. The major advantage was the bleeding are less when compare with enoxaparin/ Vitamin K antagonists Patients with acute pulmonary embolism constituted about one-third of the patients included in phase III trials with dabigatran, apixaban and edoxaban for the treatment of venous thromboembolism.

NON ANTICOAGULANT IN CANCER

In cancer patient the survival for long term as LMWHs is used. This benefit is associated in the molecular mechanism in LMWH with interruption the cell surface involving in heparan sulfate (HS) chains and matrix proteoglycans (HSPGs) as extracellular with growth factor and their receptors, heparinase and selectins. For the release of above factor in endothelium from tissue factor pathway inhibitor the beneficial effects of heparin species. Due to anticoagulant activities the use of heparin and LMWH in anticancer drug are limited. By the units of sequence, the non-anticoagulant heparin is obtained through removing the chains containing the antithrombin-binding or inactivating the critical functional groups. Through regio selectively desulphated heparins and glycol-split heparins the non-anticoagulant heparins are most extensively studied. In heparinase both types and modified heparins are potent inhibitor. In experimental model the number are attenuate as metastasis. In early stage of metastasis, it appears to be prevalent of mechanism in attenuation in vascular endothelium of interaction of tumor cells and in tumor cell platelets aggregation with cancer

cells overexpressing selectins. The selectins, heparinase have different activities in structural based on growth factor inhibition requirements. The example for non-anticoagulant application is N-acetylated, glycol-split heparin that inhibit cancer in animals' model without side effects. In mice bearing this compound used to establish in it block the tumor growth and progression in myeloma cancer (Table 1).

Antitumor activities of LMWHs

The metastasis occurs in both coagulation and complex inflammatory micro-environments for cancer progression the activation through hypothesis cascade coagulation increase the development of carcinoma been thoroughly explored and is widely accepted. Rationale supporting the evidences have been presented.[22] The LMWHs have more advantage on cancer therapy that will be acting individually. By apoptosis of cancer cells, it inhibits the tumor growth with treatment of LMWHs and also it suppresses the drug resistance by up taking the drug in chemotherapy and shows sensitivity to tumor cellS.[23] Through reversing down-regulation of tumor suppressor genes in drug-resistant cells. Inhibition of Metastasis in LMWH and UFH limit cancer progression mortality and morbidity, in cancer patients, the mechanism include: stoppage of heparinase activity, inhibition of P/L-selectin or VLA-4 integrin-mediated cell adhesion and disturbance of the inter-action between CXCR4 and CXCL12.[24]

NONANTICOAGULANT IN DERMATOSES

Lichen planus

Lichen planus are successful with treatment of LMWH with several reports are given in recalcitrant forms with immunomodulatory and anti-proliferative actions with low doses (Table 2). The tumor necrosis factor inhibit the delay of hypersensitivity reactions with very less dose and production of both are main elements in the pathogenesis of lichen planus.[25] The $CD4^+$ T cell allows to penetrate the subendothelial basal lamina with LMWH inhibit the production of heparinase. The patient with lichen planes enoxaparin a dose of 3mg/week is administered by SC and the recovery is 15 (71.4%) of 21 patients in patient with disseminated lichen planus the oral prednisone, enoxaparin 5mg/kg shows the less efficacy and less side effects. Enoxaparin shows more improvement in lichen planus when compared to conventional modalities. In lichen planus shows 13 (86.6%) of 15 patients and 12 (80%) at end of one-month study which shows good improvement in the treatment at dose of 3mg/week of enoxaparin for 20 weeks and conventional treatment are not responding. The LMWH successfully treated in hepatitis C infection with concomitant of ulcerative cutaneous lichen planus. In cutaneous lichen planus the heparinoid with topical are very effective and used as topical steroids or tacrolimus. The enoxaparin sodium in Lichen nitidus are persistent generalized reported to be successfully managed well.

Table 1: Non-anticoagulant activities of LMWHs.

Drugs	Indications	Non-anticoagulant mechanism	*In vivo/vitro**
Enoxaparin	LPS-induced systemic inflammation	Preventing histone induced cytotoxicity in leukocyte adhesion[48]	*In vivo*
	Asthma	Inhibition of cytokine release of T-cell mediated	*In vivo*
	Chronic obstructive pulmonary disease ulcerative colitis	Anti-inflammation	*In vivo*
	Liver fibrosis	Anti-inflammation maintaining the integrity of the intestinal epithelial cells interacting with pro-fibro genic mediators; suppressing expression of inflammatory cytokines; suppressing of inflammatory cytokines	*In vivo*
	Peritoneal fibrosis	Suppressing of inflammatory cytokines	*In vivo*
	Alzheimer's disease	Lowering β-amyloid plaque deposition reducing the ability of β -amyloid to activate complement and contact systems	*In vitro*
	Cancer	Increasing sensitivity of tumor cells to drugs	*In vitro*
	Sickle cell disease	Inhibiting sickle erythrocyte adhesion to VCAM-1 through VLA-4	
Bemiparin	Cancer	Inhibiting tumor metastasis by inhibition of angiogenesis	*In vitro*
Dalteparin	Endotoxin-induced systemic inflammation	Decreasing the expression of inflammation factors; diminishing sepsis-induced neutrophil sequestration; inhibiting the nuclear translocation of NF-B in the lungs	*In vivo*
	Hepatic fibrogenesis	up-regulation of hepatocyte growth factor, inhibition of hepatic stellate cells proliferation	*In vivo*
	Mild stress-induced depression	Reduction of hepcidin mRNA expression and iron content	*In vivo*
	Cancers	Inhibition of tumor growth and metastasis	*In vitro*
Nadroparin	Acetic acid-induced colitis	Modulating Nrf2/HO-1 and NF-B pathways	*In vivo*
	Hepatic fibrogenesis	Inhibiting the TGF- Smad signaling pathway	*In vivo*
	Cancers	Inhibition of tumor cell growth; preventing tumor cell adhesion, invasion and migration	*In vitro*
Parnaparin	Ulcerative colitis	Anti-inflammatory effect	*In vivo*
Tinzaparin	Cancer	Inhibition of tumor cell growth; preventing tumor cell adhesion, invasion and migration; reversing drug resistance of cancer cells[49]	*In vitro*

Chronic idiopathic urticaria

The coagulation cascade of the chronic idiopathic urticaria is associated and activate fibrinolysis in the thrombin resultant generation are involved in eosinophils and tissue factor pathways. With correlate with disease the plasma D-dimer level (markers of coagulation cascade and fibrinolytic pathway activation) are increased in chronic idiopathic urticaria as severity as well as reduced responsiveness to antihistamine.[26] In some cases the conventional therapeutic protocols is not responding in chronic idiopathic urticaria this may be probably on the effectiveness of LMWH tranexamic acid in fibrinolytics. In case of small-scale study, the patient is having improvement in chronic idiopathic urticaria were plasma elevated D-dimer and were not responsive in antihistamine, the improvement is 5(62.5%) of 8 patients in nadroparin drug and with tranexamic acid (11400 IU/day 1g thrice daily) for 2 weeks.

EFFECTS OF NON-ANTICOAGULANT ON FRACTURES

The possible involvement of heparins as a risk factor for fractures is highly controversial. In long term of LMWH several studies are calculated for the risk of fractured caused. The pettila[27] studied from pregnant population about vertebral fracture rate was 3.6% and received UFH long term and in LMWH no fracture was found. Similarly, Dahl man studied 2.2% fracture while Montreal found 15% vertebral fracture of 15% patient receiving UFH for long term comparingly 2.5% rate for LMWH for long term. The patient receiving with UFH and LMWH that confirmed the low risk of possibilities in change of bone metabolism for prominent role in this study. In bone mass density the LMWH therapy study were done for three months during fracture as per the recent meta-analysis conducted by Gajic-Veljanoski in adult populations of non-pregnant. In 24 months, that is for long term exposure there is adversely affect the BMD and the risk is low in fracture with three to six months.

EFFECTS ON BONE METABOLISM

The drug used for the bone metabolism are antagonism of Vitamin K and it produce the anticoagulant effects by inhibiting and interfering with epoxide reeducates of Vitamin K. This residue of glutamic acids carboxylation range modulates the coagulation factor II, VII, IX and X and in osteocalcin a bone-specific protein. In osteoblast the vitamin K dependent gamma-glutamyl carboxylase are localized, subsequently gamma-carboxylated synthesized in osteocalcin. The resulting of hydroxyapatite bone bind from carboxylate osteocalcin (Gla-Oc) and bone matrix accumulation. In the gamma-carboxylate incomplete with low affinity of bone matrix released into blood and influence the glucose metabolism and increased to secrete the insulin in pancreatic beta cells.

Table 2: Non-anticoagulant pharmacological activities in clinical trials.

Drugs	Indications	Study Design	Outcomes
Enoxaparin	Postoperative inflammation	Prospective trial	Reducing postoperative inflammation in patients
		Prospective trial	Lowering the total number of postoperative inflammation-related complications
	Chronic Obstructive pulmonary Disease (COPD)	Open label trial	Improvements in blood gas tensions, dyspnea and supplemental salbutamol use
		Open label trial	Benefiting the patients with COPD exacerbation during the first 14 days of treatment
	Lichen planus	Open label trial	32% had complete remission and 40% had partial improvement
	Ulcerative colitis	Open label trial	Clinical, laboratory, endoscopic, histologic and quality-of-life scores improved
		Single center randomized clinical trial (RCT)	Safe and well tolerated, but no additive benefit over standard therapy
	Liver fibrosis	Randomized, controlled, comparative study	The occurrence of hepatic decompensation delayed; survival improved
Bemiparin	Diabetic foot	Triple-blind RCT	Reduction of at least 50% in its surface area between the control at the start of treatment and at three months.[50]
Dalteparin	Ulcerative colitis	Open label trial	Most of the patients improved symptomatically and 50% attained complete remission
	Cancers	Single center RCT	Combination chemotherapy would improve in survival with LMWH treatment
		Multi center RCT	Reduction of death compared with oral anticoagulant group but not metastatic cancers
Nadroparin	Ulcerative colitis	Open label trial	The endoscopic and histological signs of inflammation improved
	Advanced cancers	Double blinded, single center RCT	Reduction of mortality at 12 and 24 months by 12% and 10% respectively and median survival prolonged from 6.6 to 8.0 months.
	Cancer	Pilot study	Longer survival was higher in the LMWH-treated group as metastasis already happened
		Multi-center, double blinded RCT	Reduction of thromboembolic events, no effect on patient survival was noted
Parnaparin	Ulcerative colitis	Multicenter RCT	Clinical remission was achieved in 83.6%
Tinzaparin	Ulcerative colitis	Prospective, double-blind, RCT	No benefit over placebo in mild to moderately active ulcerative colitis.[51]

Bone deterioration is related to dietary restrictions and it is an indirect mechanism frequently adopted in patients using VKAs.[28]

EFFECT ON BONE MINERAL DENSITY (BMD)

The three clinical trial studied was done in 237 population of pregnant woman with UFH bone and going for long term process i.e. less than 6 months and the BMD is found to reduce in significant. Barbour *et al.* for 14 pregnant women with prospective cohort studies. By means of bone densitometry the heparin therapy is required for the occurrence of heparin induced osteoporosis. In the treatment total 14 cases are include in which five (36%) have decrease in 10% from the baseline of proximal femur measurements with control study of 14 (p=0.04) this will continue for six month the significant are (p=0.03).60]. In the same manner, Douketis *et al.* found that treating with pregnant women have 7% reduction in BMD for long-term heparin therapy, while Dahlman *et al.* found that BMD reduction of 5%. The research in bone density with LMWH is less and more controversial, the studies involved in the bone density of pregnant patient population. In BMD the LMWH use was less important decrease in the patient. In enoxaparin drug (LMWH) the patient receiving for one or more year shows significant reduction in fracture.[29]

ANTI-INFLAMMATORY IN NON-ANTICOAGULANT

In the endothelium the activation of leukocytes by endothelial cell bound chemokines are stable and interfere with the every stage of leukocytes transmigration including the initial attachments with the anti-inflammatory effect of heparins which is linked into their ability. In production of different process of LMWH have the full length of the fragments and some of the molecule from LMWH have only retain for its anti-inflammatory activity.

In individual of inflammatory process have different aspect of target in LMWH. In animal and clinical studies, the LMWH shows different effects. In addition, LMWHs could further repress the expression of endothelial/monocyte cell adhesion receptors.[30-32] In Alzheimer's diseases the effects of LMWHs can be attributed partially and remaining mechanism are attribute the anti-inflammatory use and the drug used as enoxaparin[33] and the drug involved in several anti-inflammation activities and its purified fragments has its functions for reducing the ability of ß-amyloid to activate complement and contact systems and lowering A plaque deposition by decreasing the level of ß-secretase 1 (BACE1).[34-36] The mechanism underlying in non-anticoagulant treatment with LMWHs have to been detailly explained.

NON ANTICOAGULANT IN ASTHMA

The anticoagulant like glycosaminoglycan (heparin) used in the asthma clinical practice. The activation is by binds with anti-thrombin and cause different changes in its effects and inactivation of the above process involved in clotting mostly Factor Xa. In anticoagulant properties it has many use like anti-inflammatory, which include the inhibition of lymphocyte activation, neutrophil chemo taxis, smooth muscle growth, vascular tone, complement activation and also inhibition of inflammatory mediators like eosinophilic cation protein, peroxidase, neutrophil elastase and cathepsin G.[37] By using of intravenous heparin the symptoms of asthma is decreased in earlier studies.[38,39] The inhaled heparin was used for mild to severe asthma patients and no subject has improvement.[40] The inhaled heparin subsequent studies are demonstrated reduced Broncho constrictive responses in patients with exercise-induced asthma[41,42] inhaled enoxaparin (a low molecular weight heparin) demonstrated similar protective effects.[43] The nebulized heparin was used before 10 min to the subject suffering from asthma and house dust mite allergy and it inhibit the bronchospasm[44] and 5 treatments with nebulized heparin between 90 min before until 6 hr after allergen exposure attenuated the early and reduced the late allergic response.[45] However the trial was done with mixer of two drugs namely inhaled heparin and methacholine have inhibited result in bronchospasm.[46,47] The heparin at present not used for asthma attacks it is used as adjunctive therapy for clinical use and there is no complication about bleeding so for reported.

In conclusion about the asthma pathophysiology with procoagulant and anticoagulant it plays a role in cells and mediators' pathway. The asthma patient having the coagulation of activation in their airways the anticoagulant is used to reduce the coagulation for free flow of air and attenuated fibrinolysis is also decreased and by this model in mouse the inhibition of coagulation reduces the eosinophil, lung inflammation and remodeling the airways and improves the lung function. The platelets have many functions in asthma and IgE respond directly and release inflammatory mediators for aggregates with leukocytes.

In mice model the inhaled APC are administered in ovalbumin-challenged have strong anti-inflammatory effects. The protein APC induce the inhibition of coagulation and also has cytoprotective effects and the PARs have link between the coagulation and inflammation in an experimental study it proved. So, when the PARs are activated in the allergen the severity of asthma was very high by means of clotting proteases or proteases. In preclinical trial there is abundance of data are provided for the new treatment of asthma in case with severe and refractory disease. By these basic studies in pre-clinical studies it brings next level development for the new mechanism and development of novel drug treatment of asthma in clinical trials.

NON ANTICOAGULANT IN MALARIA PARASITES

The excessive sequestration of *Plasmodium falciparum* of severe human malaria attributes the infected and uninfected erythrocytes in vital organs. Strains of *P. Falciparum* has employed host receptor of heparan sulfate for the development of severe malaria. The heparan sulfate is which is used previously for same block of severe malaria and now it is stopped due to its intracranial bleeding the new form of this heparan sulfate is used with depolymerization process by heparin by periodate treatment to have new novel glycans (dGAG) which has less anticoagulant activity. In *P. falciparum* the dGAGs stops the merozoite expansion of erythrocyte and endothelial binding as an invitro and in case of *in vivo* with severe malaria it inhibit the sequestration. The 80% of dGAGs blocks the infected erythrocytes which will bind into the micro-vasculature and release the parasite into the circulation, along with the infected erythrocytes the *Macaca fascicularis* are also released into the circulation. The 500 Ig of dGAGs of injection was given in order to reduce the infected malaria.

NON-ANTICOAGULANT IN ANTI-HUMAN IMMUNODEFICIENCY VIRUS

In human immune deficiency virus (IIIV) the Novel sulfated polysaccharides, sulfated bacterial glycosaminoglycan (Org 31581) and chemically degraded heparin (Org 31733), have proved to be potent and selective inhibitors *in vitro*. The HIV type I inhibit the 50% of concentrations in MT-4 cells 0.67 and 0.52 JLg/ml, respectively. In dextran sulphate and the standard heparin, the values are compared as 0.39and 0.89 JLg/ml respectively. When compare to dextran sulfate and standard heparin the org 31581 and 31733 have less anti -thrombin activity. The sulfated polysaccharide shows anti-thrombin activity with anti-HIV. In HIV I and HIV 2 the org 31581 and 31733 were equally

inhibited and has human replication of cytomegalovirus. The org 31581 also inhibit the syncytium formation induced by co-cultivation of MOLT-4 (clone 8) cells with chronically HIV-I infected HuT 78 Cells. The org 31581 and 31733 block the host cells virus by absorption with previously demonstrated in dextran sulfate and heparin. The compound that have been used in chemotherapy of anti-HIV infections.

CONCLUSION

Based upon the above review the non-anticoagulant was used in various disease and even though the heparin is the first choice of drug in anticoagulant therapy and same manner the non-anticoagulant treatment should be first line drug for various drug should be confirm by its mechanism or by clinical trials. Still some unknown mechanism was not clarified due to its in clinical trials in patients and it should be confirmed for regular use as such like heparin.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ABBREVIATIONS

LMWH: Low Molecular Weight Heparin; **AT:** Anti Thrombin; **SAR:** Structural activity Relationship; **UF:** Unfractionated Heparin; **GlcA:** D-Glucuronic acid; **TFPI:** Tissue factor pathway inhibitor; **HC2:** Heparin cofactor II; **APTT:** Activated partial thromboplastin time; **SC**: Subcutaneous; **mg:** milligram; **HS:** heparan sulfate; **HSPGs:** Heparin sulfate matrix proteoglycans; **VLA-4:** Very Late Activating Antigen-4; **CXCR4:** C-X-C chemokine receptor type 4; **CXCL12:** C-X-C motif chemokine 12; **CD4:** Cluster of differentiation 4; **LPS:** Lipopolysaccharides; **VCAM1:** Vascular cell adhesion molecule 1; **NF-B:** Neurofibromatosis; **mRNA:** Messenger RiboNucleic Acid; **NRF2** Nuclear factor erythroid 2-related factor 2; **HO-1:** Heme oxygenase 1; **TGF:** Tumor growth factor; **IU:** International units; **BMD:** Bone Mineral Density; **COPD:** Chronic obstructive pulmonary disease; **RCT:** Randomized clinical trial; **BACE1:** Beta-secretase 1; **IgE:** Immunoglobulin E; **APC:** Argon plasma coagulation, **PARs:** Proteinase-activated receptors; **HIV:** Human Immunodeficiency Virus.

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