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A Review on Heparin Induced Thrombocytopenia in Chronic Kidney Disease

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ABSTRACT: Heparin induced thrombocytopenia remains a commonly encountered iatrogenic complications of heparin therapy in hospitalized patients. In the nearly 6 decades since the initial description of the diseases, there have been major advances in understanding the pathogenesis of HIT, its varied clinical complications and treatment. Clinician treating patients with heparin should determine platelet count at baseline and hence forth at regular intervals beginning from fifth day of therapy. We recommended commencement of warfarin therapy concurrently with heparin infusion and discontinuation of heparin once warfarin has become effective.

KEYWORDS: Heparin, thrombocytopenia, warfarin, platelet, low molecular weight heparin

I. INTRODUCTION

CHRONICKIDNEYDISEASE(CKD)

[1]. Theterm"chronickidneydisease"means damagetothekidneysand it cannot filter blood.If the damage is worse, the kidneys may stop working. This is called kidney failure, or end-stagerenal disease (ESRD). If kidneys fail, the person will require dialysis or a kidney transplant in order tosurvive.

Etiology

- Diabetes
- Highbloodpressure(hypertension)
- Heartdisease
- Havinga familymemberwithkidneydisease
- BeingAfrican-American,Hispanic, NativeAmericanor Asian
- Beingover60yearsold

2. Classification ofCKDbasedonGMRvalue

StagesofCKD	GFR	Description	Prevalencein the USA(%ofpopulation)
1	>=90ml/min+proteinurea	Kidneydamagewithnormalorincreased GFR	3.3
2	60-89ml/minproteinurea	Kidneydamagewith mildlydecreasedGFR	3.0
3	30-59ml/min	ModeratereductioninGFR	4.3
4	13-29ml/min	SeverereductioninGFR	0.2
5	<15ml/min	Kidneyfailure	0.1

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3. Symptomsofkidneyfailure

- Itching
- Musclecramps
- Nauseaandvomiting
- Notfeelinghungry
- SwellinginyourfeetandanklesToomuch urine(pee)ornotenoughurine
- Troublecatchingyourbreath
- Troublesleeping
- Backpain
- Diarrhea
- Fever
- Nosebleeds
- Rash
- Vomiting

4. ComplicationsofCKD

Someofthecommon complications ofCKDinclude:

- Anemia
- bonedisease
- heartdisease
- highpotassium
- highcalcium
- fluidbuildup

5. Stages of CKD

[2]. Chronic kidney disease (CKD) refers to 5 stages of kidney damage, from very mild damage in Stage 1to complete kidney failure in Stage 5. The stages of kidney disease are based on how well the kidneyscandotheirjob–tofilterwasteandextra fluidoutof theblood.

- Stage1withnormalorhighGFR(GFR>90mL/min)
- Stage2MildCKD(GFR= 60-89mL/min)
- Stage3A ModerateCKD(GFR=45-59 mL/min)
- Stage3BModerateCKD(GFR= 30-44mL/min)
- Stage4SevereCKD(GFR=15-29 mL/min)
- Stage5EndStageCKD(GFR<15mL/min)

6. Diagnosis of CKD

- eGFR(estimatedglomerularfiltrationrate)

[3].TheeGFR isasignofhowwellyourkidneysarecleaningyourblood.

Body makes waste all the time. This waste goes into theblood. Healthy kidneys take thewaste out ofblood. One type of waste is called creatinine. If there is too much creatinine inblood,itmightbeasignthatkidneysarehavingtroublefilteringyourblood.

- Urinetest

This testis donetoseeifthereis bloodorprotein inyoururine(pee).

kidneysmakeurine.Ifyouhavebloodorproteininyourine,itmaybeasignthat yourkidneysarenotworkingwell.

- Bloodpressure

Thistestis donetoseehowhardheartis workingtopump blood.

Highbloodpressurecancausekidneydisease,butkidneydiseasecanalsocausehighbloodpressure.Sometimeshighbloodpressureisasignthatyourkidneysarenotworkingwell.

Formostpeopleanormalbloodpressureis lessthan120/80 (120over80).

7. Treatment

[4].Damagetokidneys isusuallypermanent.Althoughthedamagecannotbefixed,youcantakestepstokeep your kidneys as healthy as possible for as long as possible.

- Controlyourbloodsugarifyouhavediabetes.
- Keepahealthybloodpressure.
- Followalow-salt,low-fatdiet.
- Exerciseatleast30minutesonmostdaysofthewee k.
- Keepahealthyweight.
- Donot smoke orusetobacco.
- Limitalcohol.
- Talktoyourdoctoraboutmedicinesthatcanhelpprotectyourkidneys.

Ifyoucatchkidneydiseaseearly,youmaybeabletoprevent kidneyfailure.Ifyourkidneysfail,youwillneeddialysis orakidneytransplanttosurvive.

8. Drugtherapy

Diuretics:

o Highceiling

Furosemide,Bumetanide,TorasemideMediumefficacy:Benzothiadiazines,

Hydrochlorothiazide,Hydroflumethiazide,Benzthiazide

o Thiazidelike

chlorthalidone,Metolazone,Xipamide,Indapamide,clopamide

o Weakoradjunctivediuretics:

Carbonicanhydraseinhibitor-AcetazolamideOsmotic diuretic -Mannitol, isosorbide, GlycerolPotassiumsparingdiuretics: AldosteroneantagonistRenalepithelialNa+channelinhibitors: Amiloride

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Hyperkalemia

1. Iv10%calciumgluconate
2. Raisesthresholdforexcitation
3. Sodiumbicarbonate
4. Shift potassiumintocells
5. Correctacidosis
6. Sodiumpolystrenesulfonate
7. Cation exchangeresin
8. Resin inbowelexchangepotassium
9. Evacuatepotassiumrichstool frombody
10. Educatepatient thatdiarrheamayoccurduetolaxative.

[5]. Drugs associated with increased serum levels of potassium, such as beta-blockers,mineralocorticoids receptor antagonists, calcineurin, nonsteroidal anti-inflammatories, trimethoprim,andheparinshouldbeadjustedorre placedinthe occurrenceof thiscomplication

Hypertension

1. Antihypertensivedrugs
2. Diuretics
3. Betaadrenergicblockers
4. Calciumchannelblockers
5. Angiotensinconvertingenzymeinhibitors
6. Angiotensinreceptorblockeragents.

Hypertensionis bothacommonresultandafrequent causeofchronickidneydisease.It may be prevented by adequate treatment, thereby preventing a further decline inrenalfunction.

Renalosteodystrophy

1. Phosphateintakerestrictedto<1000mg/day
2. Phosphatebinder
3. Calciumcarbonate
4. Bindphosphateinbowelandexcreted
5. Sevelamer hydrochloride
6. LowercholesterolandLDLS

[6].

Renalosteodystrophydescribesthefourtypesofb onediseaseassociatedwithchronickidneydisease :

I. Secondaryhyperparathyroidism
II. Osteomalacia
III. Mixedrenalosteodystrophy
IV. Adynamicbonediseas

Anemia

1. Erythropoietin
2. Epoetinalfa
3. AdministeredIVorsubcutaneously
4. Increasedhemoglobinandhematocietin2to

3.Weeks

[7]. Complications

1. Hypertension
2. Headache
3. Ironsupplement
4. Ifplasma fruectin<100mg/ml

Sideeffect

1. Gastricirritation,constipation
2. Maymakestooldarkincolor
3. Follicacidsupplement
4. NeededforRBCformation
5. Removedbydialysis
6. Avoidbloodtranslution
7. Nutritionaltherapy
8. Proteinrestriction
9. Waterrestriction

9. Treatingcomplications

[8]. Kidneydiseasecomplications canbecontrolledtomakemorecomfortable.Treatment smayinclude:

- High blood pressure medications.People with kidney disease may experience worseninghigh blood pressure. Your doctor may recommend medications to lower your blood pressure — commonlyangiotensin-convertingenzyme(ACE)inhibitorsor angiotensinIIreceptorblockers

— and to preserve kidney function. High blood pressure medications can initially decreasekidney function and change electrolyte levels, so you may need frequent blood tests to monitoryour condition. Your doctor will likely also recommend a water pill (diuretic) and a low-saltdiet.

- Medications to lower cholesterol levels.Your doctor may recommend medications calledstatins to lower your cholesterol. People with chronic kidney disease often experience highlevelsof badcholesterol,whichcanincreasetheriskofheart disease.
- Medications to treat anemia**.** In certain situations, your doctor may recommendsupplements of the hormone erythropoietin (uh-rith-roe-POI-uh-tin), sometimes with addediron.Erythropoietinsupplements aidinproductionofmoreredbloodcells,which mayrelievefatigueandweaknessassociatedwitha nemia.
- Medications to protect your bones.Your doctor may prescribe calcium and vitamin Dsupplements to prevent weak bones and lower your risk of fracture. You may also

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takemedicationknownasaphosphatebindertolo wertheamount ofphosphateinyourblood,andprotectyourbloodv esselsfromdamagebycalciumdeposits(calcificat ion).

- Alowerproteindiettominimize wasteproductsinyourblood.Asyourbodyprocess es protein from foods, it creates waste products that your kidneys must filter from yourblood. Your doctor may also ask you to meet with a dietitian who can suggest ways toloweryourproteinintake whilestilleatingahealthydiet.

10. Treatmentforend-stagekidneydisease

Ifyourkidneys can't keep up withwasteandfluidclearanceontheirownandyou developcompleteor near-complete kidney failure, you have end-stage kidney disease. At that point, you need dialysisora kidneytransplant.

- [9]. Dialysis. Dialysis artificially removes waste products and extra fluid from your blood whenyourkidneyscannolongerdothis.Inhemodi alysis,amachinefilterswasteandexcess fluidsfrom your blood. r aperiodoftime,thedialysissolutiondrains fromyourbody,carryingthewastewith it.
- Kidneytransplant**.**Akidneytransplant involvessurgicallyplacingahealthykidneyfroma donor into your body. Forsomewhochoosenottohavedialysisorakidne ytransplant,athird optionis totreatkidneyfailure with conservative measures. Potentialfuturetreatments

Regenerativemedicineholdsthepotentialtofullyheald amagedtissuesandorgans,offeringsolutionsandh opeforpeople whohaveconditionsthattodayare beyondrepair.

Regenerativemedicineapproachesinclude:

- Boostingthebody'snaturalabilitytohealitself
- Usinghealthycells,tissuesororgansfromalivingo rdeceaseddonortoreplacedamagedones
- Delivering specific types of cells or cell products to diseased tissues or organs to restore tissueandorganfunction.

11 Patientcounseling

Lifestyleandhomeremedies

As part of your treatment for chronic kidney disease, your doctor may recommend a special diet tohelpsupport yourkidneysandlimittheworktheymustdo.

Askyourdoctorforareferraltoadietitianwhocananalyz eyourcurrentdiet andsuggestways tomakeyourdieteasieron yourkidneys.Dependingonyoursituation, kidneyfunctionandoverallhealth,yourdietitianmayre commendthatyou:

- [10]. Avoidproductswithaddedsalt.Lowertheamount ofsodiumyoueateachdaybyavoidingproducts with added salt, including many convenience foods, such as frozen dinners, cannedsoups and fast foods.Other foods with added salt include salty snack foods, canned vegetables,andprocessedmeatsandcheeses.
- Choose lower potassium foods**.** Your dietitian may recommend that you choose lowerpotassium foods at each meal. High-potassium foods include bananas, oranges, potatoes,spinach and tomatoes. Be aware that many salt substitutes contain potassium, so yougenerallyshouldavoidthemif youhavekidneyfailure.
- Limit the amount of protein you eat.Your dietitian will estimate the appropriate numberof grams of protein you need each day and make recommendations based on that amount.Highprotein foods include lean meats, eggs, milk, cheese and beans. Low-protein foods includevegetables,fruits,breadsandcereals.

12 PreventionofCKD

[11]. If the patient is havingdiabetes or high blood pressure, working with doctor to keep the blood sugar and blood pressureundercontrolisthebestwaytopreventkidneyd isease.

Living a healthy lifestyle can help prevent diabetes, high blood pressure and kidney disease, or helpkeepthemundercontrol.Followthesetips toloweryourriskforkidney diseaseandtheproblems thatcauseit:

- Followalow-salt,low-fatdiet
- Exerciseatleast 30minuteson most days oftheweek
- Haveregularcheck-upswithyourdoctor
- Donotsmokeorusetobacco
- Limitalcohol

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13. HEPARIN

[12]. Heparin is a sulfated polysaccharide with a molecular weight range of 3000 to 30 000 Da(mean, 15 000 Da).Heparin is used to treat and prevent blood caused by certain medicalconditions or medical procedures. It is also Certain medicines can increase your risk ofbleeding while you are using heparin, such as aspirin or other NSAIDs (nonsteroidal anti-inflammatory drugs) including ibuprofen (Advil, Motrin), naproxen (Aleve, Naprosyn,Naprelan, Treximet), celecoxib (Celebrex), diclofenac (Arthrotec, Cambia, Cataflam,Voltaren, Flector Patch, Pennsaid, Solareze), indomethacin (Indocin), meloxicam (Mobic),ketoprofen(Orudis),ketorolac(Toradol),mefenamicacid(Ponstel),nabumetone(Relafen),piroxicam (Feldene), and others. Thisincludes prescription, over-the-counter, vitamin, and herbal products. Do not start a newmedicationwithouttellingyourdoctor.beforesurgerytoreducetheriskofbloodclots.

Formsofheparin

Unfractionalheparin

Lowmolecularweightheparin
Mechanismofaction

It produces its major anticoagulant effect by inactivating thrombin and activated factor X (factorXa) through an antithrombin (AT)-dependent mechanism. Heparin binds to AT through a highaffinitypentasaccharide,whichispresentonabout a third of heparin molecules. For inhibition of thrombin, heparin must bind to both thecoagulation enzyme and AT, whereas binding to the enzyme is not required for inhibition offactor Xa. Molecules of heparin with fewer than 18 saccharides lack the chain length to bridgebetween thrombin and AT and therefore are unable to inhibit thrombin. In contrast, very smallheparin fragments containing the pentasaccharide sequence inhibit factor Xa via AT. Byinactivating thrombin, heparin not only prevents fibrin formation but also inhibitsthrombininducedactivationofplateletsandoffactorsVandVIII.

- [13]. The main limitation of heparin results from its propensity to bind to positively chargedproteins and surfaces. Pharmacokinetic limitations are caused by AT-independent binding ofheparin to plasma proteins, proteins released from platelets, and endothelial cells, resulting inavariableanticoagulant responseandthephenomenonofheparinresistance.AT-independentbinding to macrophages and endothelial cells also results in dose-dependent clearance. Otherlimitations include (1) the inability of heparin to inactivate factor Xa in the prothrombinasecomplex or thrombin bound to fibrin or to subendothelial surfaces and (2) the complicationsofheparin-inducedthrombocytopeniaandosteopenia.

- Because the anticoagulant response to heparin varies among patients with thromboembolicdisorders, it is standard practice to adjust the dose of heparin and monitor its effect bymeasurementoftheactivatedthromboplastintime(APTT)or,whenveryhighdosesareused,bytheactivatedclottingtime(ACT).
- The value of the APTT is limited because commercial APTT reagents vary considerably inresponsiveness to heparin. The APTT should be measured ≈6 hours after a bolus dose ofheparin, and the continuous intravenous (IV) dose should be adjusted according to the result.Various heparindose-adjustment nomograms have been developed, but none are applicable toall APTT reagents, and the therapeutic range must be tailored accordingly. Standardizationcan be achieved by calibration against plasma heparin concentration by using a therapeuticrangeof0.3 to0.7U/mL,based onananti–factorXachromogenicassay,oraheparin levelof 0.2 to 0.4 U/mL, by protamine sulfate titration. The dose of heparin should be reduced whenusedconcurrentlywithfibrinolytic agentsorIV plateletglycoprotein(GP)IIb/III receptorantagonists.

14. DrugTherapy

- [14]. Anticoagulants:parenteralanticoagulants
- Indirectthrombininhibitors-Heparin,lowmolecularweightheparins(Enoxaparin,Reviparin,Dalteparin) Fondaparinux,Danaparoid
- Directthrombininhibitors-lepirudin,Bivalirudin,Argatroban
- Oralanticoagulant:Directfactor XainhibitorRivaroxaban
- Oraldirectthrombininhibitor :Dabigatranetexilate
- Coumarinderivatives:warfarinsodium,Acenocoumarol,Ethylbiscoumacetate

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- Invitroanticoagulants:Heparin,sod.edetate,sod. citrate,sod.oxalate

15. Pharmacology

[15].Heparinisgivenparenterally becauseitisnotabsorbedfromthegut,duetoitshighnegative charge and large size. Because of its short biologic half-life of about one hour, heparin mustbe given frequently. Unfractionated heparin has a half-life of about one to two hours afterinfusionwhereasLMWHhas ahalf-lifeoffourtofivehoursTheuseofLMWHhasallowed once-daily dosing, thus not requiring a continuous infusion of the drug. If longtermanticoagulation is required, heparin is often used only to commence anticoagulation therapyuntilanoralanticoagulante.g.warfarintakeseffect.

The anticoagulant activity of heparin is mainly attributable to the action of a specificpentasaccharidesequencethatactsinconcert withantithrombin, aplasmacoagulationfactorinhibitor. However, it is increasingly recognized that heparin has many otherpharmacological properties, including but not limited to antiviral, anti-inflammatory, andantimetastatic actions. Many of these activities are independent of its anticoagulant activity,althoughthemechanismsoftheseotheractivitiesarecurrentlylesswelldefined.
Nonetheless, heparinisbeingexploitedforclinicalusesbeyondanticoagulationanddevelopedfora widerangeof clinicaldisorders.

16. Pharmacokinetic:

Heparin binds reversibly to its target sites of action, antithrombin and the other serine proteasesinvolvedincoagulation, especiallyactivatedfactorX.Italsobindstootherplasma proteins,includingfibrinogen, plasmin, albumin, and lipases. The volume of distribution of heparin is then, under mostcircumstances, limited to the plasma volume In all likelihood, theanticoagulant is transferred to reticuloendothelial cells, which may also provide the means for itsdegradation. Many of the difficulties inherent in assessing the kinetic properties of heparin, as well asitsclinicalefficacy,maybeattributedto:

(1) [16]. itsmolecularheterogeneity;

(2) itswidespectrumofbindingsitesandtheirrespectivekineticpropertiesanddissociationconstants;

(3) differencesamongmethodsformeasuringheparin effectandconcentration;

(4) thedosedependenceofthedrug's half-life;

(5) variationinpatientresponsetoheparin;

(6) thespecificcationassociatedwithit;and

(7) thepresenceofhypercoagulationsyndromesassociatedwithdeficitsofantithrombin.

Neither renal nor hepatic disease, nor the biological tissues from which heparins are extractedcommercially, seem to influence the drug's kinetic properties as much as variations in clearance andresponse to heparin among individual patients. Many comparisons among available studies aredifficult because of the wide variation in the assay methods employed in them. It would appear thatoptimum therapy with heparin can be achieved only when the individual patient's response to, and rateofeliminationof,heparinaretakenintoaccountconcurrently.
Absorption: Heparin is not absorbed from GI, must be given IV or subcutaneously.
Metabolism: metabolized in liver and reticuloendothelial system .
Elimination: The average half life is 1.5 hrs and is dose dependent excreted in the urine.

Naturaldegradationorclearance:

[17]. Lower doses of heparin havea much shorter half-life than larger ones. Heparin binding to macrophage cells isinternalized and depolymerized by the macrophages. It also rapidly binds to endothelialcells, which precludes the binding to antithrombin that results in anticoagulant action. Forhigher doses of heparin, endothelial cell binding will be saturated, such that clearance ofheparinfromthebloodstreambythekidneyswillbeaslowerprocess.

Dosageandadministration

- Intravenously,20 to40000unit/daydose
- Subcutaneously,8000 to10000units every8h

Contraindications

- Severethrombocytopenia
- Patient in whomsuitablebloodcoagulationtest cannotbeperformed
- Hypersensitivitytoheparinoranyotherproductin

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gredients
- Donotadministerproduct containingbenzylalcoholasapreservativetoneonates,infants,pregnantwomen,orbreastfeedingwomen
- Patientswithhypersensitivitytoproduct andbisulfates

Management
Heparin has an immediate effect on blood clotting but it act for only 4-6hours.The effect of anheparinisbest assessedbyAPTT.Act byactivatingantithrombinandinactivatesXa,1Xaetc
- [18]. Consult the physician to determine the safety of stooping heparin during postoperativeperiods.
- Delaythesurgeryfor6hours afterstoopingheparin oruseofheparinantagonistlikeprotaminesulphate.
- Startheparinonceagoodclot isformed.

Druginteraction
[19]. Interactionwith:Alteplase

AntihistaminesAntithrombinCephalosporinPencillinParenteral
Interactions
- Prophylaxisandtreatment ofvenousthromboembolismandpulmonaryembolism;
- Atrialfibrillationwithembolization;
- Preventionofclottinginarterialand cardiacsurgery;
- Prophylaxisandtreatmentofperipheralarterialembolism;
- Anticoagulantuseinbloodtransfusions, extracorporealcirculation,anddialysisprocedures.

Adversereaction
- Hematologic
- Cardiovascular
- Dermatologic
- Musculoskeletal
- Endocrine

ClinicalUseof Heparin
[20]. Heparin is effective for prevention and treatment of venous thrombosis and pulmonaryembolism (PE), for prevention of mural thrombosis after myocardial infarction (MI), and fortreatment of patients with unstable angina and MI. Although heparin is used to prevent acutethrombosisaftercoronarythrombolysis,recent reportsquestionthebenefitsofheparininthissettingwhenpatientsarealsotreatedwithaspirin

17. THROMBOCYTOPENIA

Thrombocytopenia is a condition in which it shows low blood platelet count. Platelets(thrombocytes)arecolorless bloodcellsthathelpbloodclot.Plateletsstopbleedingbyclumpingandformingplugsinbloodvesselinjuries. Thrombocytopenia might occur as a result of a bone marrow disorder such as leukemia or an immunesystem problem. It affects both children andadults. .Thrombocytopenia can be mild and cause few signs or symptoms. In rare cases, the number ofplateletscanbesolowthatdangerousinternalbleedingoccurs.
[21].
Plateletsinitiateasequenceofreactionsthateventuallyleadtotheformationofabloodclot.
Thrombocytopenia is lower than a normal number of platelets (less than 150,000 platelets permicroliter)intheblood.Normalplatelet counts rangefrom150,000 to400,000 permicroliterintheblood.
Plateletsareoneofthecellularcomponentsoftheblooda longwithwhiteandredbloodcells.Plateletsplay an important role in clotting and bleeding. Platelets are made in the bone marrow similar to othercells in the blood. The fragments of these megakaryocytes are platelets that are released into the bloodstream.The circulating platelets make up about two-thirds of the platelets that are released from the bonemarrow. The other third is typically stored (sequestered) in the spleen **Signs and symptoms mayinclude:**
- Thrombocytopeniaor lowplateletcountislower thananormalnumber ofplatelets(lessthan150,000plateletspermicroliter) intheblood.
- Thrombocytopeniamaybeinheritedoracquiredwhenconditionsoccur,suchastheuseofcertaindrugs.
- Causes of thrombocytopenia can be classified into three groups: o Diminished production(caused by viral infections, vitamin deficiencies, aplastic anemia, drug-induced) o Increaseddestruction(causedbydrugs,heparin

[HIT], idiopathic, pregnancy, immune system) o Sequestration (caused by anenlargedspleen,neonatal,gestational,pregnancy)

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- Thrombocytopenicsymptomsmayinclude:

  - Petechiae(superficialtinyareasof bleedingintotheskinresultinginsmallreddishspots)
  - Fatigue
  - Purpura(easyorexcessivebruising)oProlongedbleedingcuts
  - SpontaneousbleedingfromthegumsornoseoJaundice
  - Heavymenstrualbleedingthat'sunusualforthefemale
  - Blood in the urine or stools o Enlarged spleen (splenomegaly) o Bleeding thatwillnotstopoDVT(deepveinthrombosis)
- Individuals shouldseekmedicalcareiftheyhaveoneormoreofthesesymptoms.
- Doctorsthatmaybeconsultedfor thrombocytopenia includeemergencymedicine,internalmedicine,hematologists,andimmunologists.
- Thediagnosisofthrombocytopeniaisconfirmedbybloodteststhatdetermineplateletcount.
- Treatmentofthrombocytopeniavaries dependingonthecauseandtheseverity ofthecondition.
- Complicationsofthrombocytopeniacanbesevere (organdamageanddeath).
- Iftreatedearlyandeffectively, theprognosisforthrombocytopeniaisusuallygood. However,ifdiagnosedlaterinthediseaseprocess,orifHIT isthecause,theprognosisdecreases.

Causes

- Thrombocytopeniameans youhavefewerthan150,000plateletspermicroliterofcirculatingblood. Because each platelet lives only about 10 days, your body normally renews yourplateletsupplycontinuallybyproducingnew plateletsinyourbonemarrow.
- [22]. Thrombocytopenia rarelyisinherited;oritcanbecausedbya numberofmedicationsorconditions. Whatever the cause, circulating platelets are reduced by one or more of thefollowingprocesses:

trappingofplatelets inthespleen,decreased

plateletproductionorincreaseddestructionofplatelets.

- It has has many causes. You may hear it called by its old name, idiopathicthrombocytopenicpurpura.Althoughdoctorsdon't knowwhatcausesprimaryITP,theyknowthat it happens when your immune system -- your body's main defense against disease --doesn't work right. Your antibodies, which are supposed to attack infections, insteadmistakenlydestroyyourplatelets.

Trappedplatelets

Thespleen is asmallorganaboutthesizeofyourfistsituatedjust belowyourribcageontheleft sideof your abdomen. Normally, your spleen works to fight infection and filter unwanted material fromyour blood. An enlarged spleen — which can be caused by a number of disorders — can harbor toomanyplatelets,whichdecreasesthenumberof plateletsincirculation.

Decreasedproductionofplatelets

Plateletsareproducedinyourbonemarrow.Factorsthat candecreaseplateletproductioninclude:

- Leukemia andothercancers
- Sometypesofanemia
- Viralinfections,suchashepatitisC orHIV
- Chemotherapydrugsandradiationtherapy
- Heavyalcoholconsumption

Increasedbreakdownofplatelets

Someconditionscancauseyourbodytouseup ordestroyplatelets fasterthanthey'reproduced,leadingtoashortageofplatelets inyourbloodstream.Examplesofsuchconditionsinclude:

- Pregnancy. Thrombocytopeniacausedbypregnancyisusuallymildandimprovessoonafterchildbirth.
- Immune thrombocytopenia. Autoimmune diseases, such as lupus and rheumatoid arthritis, causethistype.Thebody'simmunesystemmistakenlyattacksanddestroysplatelets.Iftheexactcause of this condition isn't known, it's called idiopathic thrombocytopenic purpura. This typemoreoftenaffectschildren.
- Bacteriaintheblood.Severebacterialinfections involvingtheblood(bacteremia)candestroyplatelets.
- Thromboticthrombocytopenicpurpura.This is arareconditionthatoccurs whensmallbloodclots suddenlyformthroughoutyourbody,usinguplargenumbersofplatelets.
- Hemolyticuremicsyndrome. Thisraredisordercausesasharpdropinplatelets,

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destructionofredbloodcellsandimpairskidneyfunction.
- Medications. Certainmedicationscanreducethenumberofplateletsinyourblood.Sometimesadrugconfusestheimmunesystemandcausesitto

destroyplatelets.Examplesincludeheparin,quinine,sulfa-containingantibioticsandanticonvulsants.

Drugtherapy
- Thromboxanesynthesisinhibitor:Aspirin
- PlateletcAMPenhancer:Dipyridamole
- P2Y12receptorblockers:Ticlopidine,clopidogrel
- Gpantagonist:Abciximab,Eptifibatide

Complications

[23]. Internal bleeding is very dangerous whereas platelet count falls below 10,000 platelets permicroliter.Severethrombocytopeniacancausebleedingintothebrain.

Diagnosis
- Bloodtest.Acompletebloodcount determinesthenumberofbloodcells,includingplatelets,inasample ofyourblood.
- Physical exam, including a complete medical history. He or shewill also ask you about illnesses you've had and the types of medications and supplementsyou'verecentlytaken.

Treatment

Thrombocytopenia can last for days or years. People with mild thrombocytopenia might notneedtreatment.For peoplewhodoneedtreatmentfor thrombocytopenia,treatmentdependsonitscauseandhowsevereitis.

If your thrombocytopenia is caused by an underlying condition or a medication, addressingthat cause might cure it. For example, if you have heparin-induced thrombocytopenia, yourdoctorcanprescribeadifferentblood-thinningdrug.Othertreatmentsmight involve:

- Blood or platelet transfusions. If your platelet level becomes too low, your doctor can replacelostbloodwithtransfusionsof packedredbloodcellsorplatelets.

18. HEPARININDUCEDTHROMBOCYTOPENIA

- [24]. Heparin-induced thrombocytopenia (HIT) is the development of thrombocytopenia(a low plateletcount), due to the administration of various forms of heparin, an anticoagulant. HIT predisposes tothrombosis (the abnormal formation of blood clots inside a blood vessel) because platelets releasemicroparticles that activate thrombin, thereby leading to thrombosis. When thrombosis is identifiedthe condition is called heparin-induced thrombocytopenia and thrombosis (HIT). If someone receiving heparin developsneworworseningthrombosis,orifthepla telet count falls,HITcanbeconfirmedwithspecificbloodtests.
- ThetreatmentofHITrequiresstoppingheparintreatment,andbothprotectionfromthrombosisandchoice of an agent that will not reduce the platelet count any further. Several alternatives areavailableforthispurpose;mainlyusedare:

Danaparoid,Fondaparinux, Argatroban,Bivalirudin

Etiology

Heparin-induced thrombocytopenia (HIT) is caused by antibodies that bind to complexes of heparinandplateletfactor4(PF4),activatingtheplatelets andpromotingaprothromboticstate.

HITismorefrequently encountered with unfractionated heparin (UFH) than with low molecular weight heparin(LMWH).

TheriskofHITishighestwith prolonged useofheparin forpostoperativethrombophylaxis.However, casestudieshavealsodemonstratedthepossibilityofdevelopingHITwithminimal heparinexposureviaintravascularflushes tomaintainthepatencyofindwellingarterialorvenouscatheters.

Fondaparinux is a synthetic pentasaccharide that catalyzes the inhibition of factor Xa (but notthrombin) by antithrombin, and thus inhibits thrombin generation. A study suggested thatfondaparinux may be associated with formation of anti–PF4/heparin antibodies but, in contrast toLMWH, is unlikely to cause HIT because of the poor reactivity of antibodies againstPF4/fondaparinux.

Pathophysiology

Heparin-induced thrombocytopaenia is defined as a decrease in platelet count during or shortlyfollowing exposure to heparin [1]. Although it is almost a century since the discovery of heparin, thedefining features of HIT were first described in the early 1970s [2] followed by increasing reports of acondition suspected to have an underlying immunological basis. We now know

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that HIT is apotentially devastating immune-mediated reaction caused by the development of IgG antibodiesagainst the complex of heparin and platelet factor 4 [3]. IgG/PF4/heparin complexes bind and activatecirculating platelets through their Fc receptors promoting thrombin generation and plateletaggregation. Paradoxically, this is clinically manifested by an increased propensity for arterial/venousthrombosis despite a falling platelet count. The condition often will affect patient groups who arealready at an increased thrombotic risk due to their clinical predicament such as those with renalfailure or requiring renal replacement therapy. Such patients will often have coexistent causes forthrombocytopaeniaotherthanHIT.

Complications

PossiblecomplicationsofHITincludethefollowing:

- Deepvenousthrombosis
- Pulmonaryembolism
- Myocardialinfarction
- Occlusionoflimbarteries(possiblyresultinginamputation)
- Transient ischemicattackandstroke
- Skinnecrosis
- End-organdamage(eg,adrenal,bowel,spleen,gallbladder,orhepatic infarction;renalfailure)
- Death

Epidemiology

In the United States, approximately 12 million individuals, or one third of hospitalized patients, havesome heparin exposure yearly. A study by Smythe and colleagues estimated the frequency of heparin-induced thrombocytopenia (HIT) to be 0.76% in patients receiving therapeutic doses of intravenousunfractionated heparin (UFH) and less than 0.1% in patients receiving antithrombotic prophylaxiswithsubcutaneousUFH,withanoverallriskofHITofabout0.2%inallheparin-exposedpatients. Otherstudiesintheliteraturequotefrequenciesashigha s1-5%.HighfrequenciesofHITareespeciallycommoninsurgicalpatientsreceivingprolongedpostoperativethromboprophylaxis(eg,for10-14 days following orthopedic surgery or after coronary artery bypass and/or valve replacementsurgery.)Mortality/Morbidity

HITisasevereprothromboticcondition, withaffectedindividualshavingagreaterthan50%riskofdeveloping new thromboembolic events. The mortality rate is approximately 20%, andapproximately 10% of patients require amputations or suffer other major morbidity.A consecutivestudy with 108 hospitalized patients diagnosed with HIT showed that thrombotic complicationsoccurred in about 29%. Early, severe falls in platelet counts in elderly patients receiving heparinappeartobeassociatedwiththedevelopmentof thromboticcomplications.

Thrombosis associated with HIT can involve the arterial system, the venous system, or both.Thrombotic complications may include deep venous thrombosis, stroke, myocardial infarction, limbischemia, and, rarely, ischemia of other organs. The thrombotic complications are fatal in about 29%of patients, and an additional 21% have to undergo limb amputations.Although HIT is ahypercoagulable disorder, patients remain at risk for major bleeding. A review by Pishko et al foundthat over a third of patients with HIT who were exposed to an alternative anticoagulant experienced amajor bleeding event.

Diagnosis

HITisaclinical–pathologicalsyndromewhereanobservedfallintheplatelet countshouldpromptthecliniciantofirstweighthelikelihoodofadiagnosisofHITonclinicalgrounds.The 4T scoring system is most widely known and is used to assess how compatible the clinical pictureis with a diagnosis of HIT . Interestingly, scoring systems used to assess the clinical pre-testprobability of HITmay underscore patients who have a similar likelihood for both HIT and othercausesforthrombocytopaeniasuchaspatientswithrenalfailure.Because of the challenges of clinical diagnosis, physicians rely heavily on laboratory testing;however, it is important to recognize that HIT antibody formation may occur without consequentialthrombocytopeniaandthefullclinicalHITpicture.

Laboratorytestingto detectantibodyformationinHITcanbe

broadly classified into platelet activation assays or immunological assays targeted towards PF4 orheparin. Functional tests, which measure platelet activity in the presence of the patient's serum andheparin, e.g. heparininduced platelet aggregation and the serotonin release assay offer greaterspecificity; however, these tests are complex and technically demanding. Consequently, most centrestend to perform the ELISA with the limitation that low titre antibodies of no clinical significance maybe detected. As it is only IgG antibodies that activate platelets, IgG-specific immunological assays arenow commercially

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available. A further consideration in interpreting the test results relates to theabsoluteoptical density (OD)values,amarkerofantibodylevelswhereincreased levelscorrespondto a greater risk of HIT. The 2012 BCSH Guidelines suggest that a cut-off point for a positive testshould be used when using an immunological ELISA to look for HIT antibodies, rather than simplyreporting a positive or negative . A retrospective study of the trend of sequential quantitative resultsobtained using an ELISA immunoassay showed that initial high negative OD values (0.7–1.0) have asignificantchanceofbecomingclearlypositive(>1.0) withrepeattestingsuggestingsequentialtestinginsuch cases.

A pre-testprobability of at least 4 using the 4T Scoring System should be taken together with the type of assayused and the quantitative result to determine a post-test probability. In routine clinical practice, asmany clinicians do not have direct access to the complete portfolio of laboratory assays, it would bereasonabletodiscusssuspectedcasesandinvestigationwiththehaematologyteamandlaboratory.

Once clinically suspected, the principles of treatment involve cessation of all heparin formulations andinitiation of an appropriate alternative anticoagulant. Discontinuation of the trigger alone is notsufficient as there needs to be targeted treatment against the thrombin storm as well as protectionagainst subsequent thrombotic events, which occur in as many as 40–50% of the patients over the nextseveral days or weeks.Reflex platelet transfusion directed toward thrombocytopaenia or minorbleeding is also contraindicated and should only be reserved for life-threatening haemorrhage to avoidpotentialexacerbationof thrombotic risk.

If HIT is suspected in a dialysis patient, dialysis needs to be performed heparin free. However, saline infusions are labour intensive andseem to have a high treatment failure rate and daily dialysis is not always feasible. Using one of theavailable alternative anticoagulants might be a more long-term option. Currently, three non-heparinanticoagulants that do not cross-react with HIT antibodies, danaparoid, lepirudin and argatroban areavailableforanticoagulationinHIT.

Where HIT occurs with unfractionated heparin, LMWH should not be used as an alternative due to upto 50% crossreactivity. Although the HIT syndrome in itself is rarely associated with bleeding, thealternative anticoagulant treatment options carry a bleeding risk and therefore should be carefullychosen.

Theidealalternativeforpatientsonhaemodialysismightbeargatroban,asyntheticthrombininhibitor, asitisnotexcretedbythekidneysanddoesnotrequirerenaldoseadjustment.Monitoring is recommended using the activated partial thromboplastin time (APTT) aiming for atarget range of 1.5– 3.0. Standard initial dosing is 2 ug/kg/min as a continuous infusion except forcritical care patients where the SmPC suggests 0.5 ug/kg/min. Standard initial dosing is recommendedas a continuous infusion except for critical care patients where the SmPC provides a reduced dosingregimen. It remains unclear if argatroban is dialysable. Whilst one author demonstrated thatthere was only an insignificant amount of argatroban removed through dialysis compared withendogenousclearance,theproduct labellingsuggeststhat 20% of the drug can be cleared throughhaemodialysis.

Danaparoidcanalsobeusedhowever;patientswithsignificantrenaldiseaseshouldreceivereduceddosingregimens.Danaparoidisaconjugateofheparinsulphate,dermatansulphateand chondrotoin.

Treatment

[25]. Relativeto heparin, danaparoid has an increased antifactor Xa: anti-factor IIa activity of around 28:1 versus1:1. The drug has a predictable dose response and therefore monitoring is usually only required incertain patient populations, in particular those with severe renal disease and body weight less than orgreater than 55 or 90 kg, respectively. Prophylactic and therapeutic dosing regimens are available;however, studies suggest that low-dose regimes may be associated with a higher rate of newthrombotic events. Monitoring is performed using the anti-Xa assay using danaparoid sodium as thestandard. The use of danaparoid has been studied in critically ill patients and those undergoinghaemofiltration/haemodialysis. Example regimes for haemofiltration include 100–400 U/h iv toachieve anti-Xa levels of 0.5–1 U/mL and 40 U/kg iv for haemodialysis.Example regimes forhaemofiltrationandhaemodialysishavebeenreported.Itis notknownifdanaparoidis dialysable.

Lepirudin, a recombinant hirudin, is a natural thrombin inhibitor and has been shown to reduce therisk of death, new thromboembolic complications and limb amputation during treatment. Standarddosing consists of 0.4 mg/kg bolus followed by 0.15 mg/kg/hr and standard

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dosing consists of a bolusfollowed by an infusion and monitoring employs the APTT aiming for a range of 1.5–2.5. Lepirudinshould not be given if the APTT is >2.5 times the normal. The t1/2of lepirudin is significantlyprolonged with reduced renal function and therefore 50% reduced dosing for bolus and infusion isadvised where creatinine levels are 1.5–2.0 mg/dL and further caution with greater renal impairment.For dialysis patients, where the t1/2is around 50 h, altered doses have been advised pre-dialysis tosuccessfully maintain anticoagulation through dialysis . Lepirudin is dialysable if used with high-fluxpolysulfonedialysers.

Although unlicensed in HIT, fondaparinux, a synthetic polysaccharide, has been used favourably inpatients with HIT. It lacks the sugar domain necessary to complex with PF4, making the likelihood ofinducingHITextremelylow.Anumberofreportsexistdetailingitsfavourableuse inHIT,inpatientswith renal failureand on haemodialysis.The initial daily dose is as per usual (7.5 mg/d for a patientweighingbetween50and100kg),butanti-Xalevelsareusedtojudgesubsequentdoses. Maintenancedosesmayonlyrequire2.5or5mgdaily.prospective studies suggestthat the risk for thrombosis can persist for up to 6 weeks; therefore, a minimum of 2 months has beenadvised. Warfarin initiation can be considered once the platelet count has returned to baseline using aregimeoverlappingwiththespecificalternativeanticoagulantthatthepatienthas beenreceiving. Discontinuationofheparinandinitiationofwarfarinaloneisnot recommendedbecauseofreports ofvenous limb gangrene most likely secondary to warfarin induce protein C depletion combined withtheongoingthrombotic process.

Finally,it isworthwhiletoprovideaffectedpatientswithinformationabout theirconditionandadvicenot only about the risk of thrombosis in the acute setting but also to highlight that should they requireheparin in the next 120 days, antibody testing may be required as well as the use of alternativeanticoagulation. As with other drug-induced adverse events, the patient's case notes should be markedtoadviseclinicians of futurerisk.Accurate recognition, evaluation and appropriate treatment of HIT in renal patients remain aconsiderable challenge and an optimal management regime is not yet backed by sufficient clinicalevidence. Due to the low diagnostic specificity of the widely applied PF4-dependent immunoassays tolook for HIT antibodies, ironically there has been a recent epidemic in over-diagnosing HIT. Testingonly for IgG class antibodies where the more specific functional assays are not available shouldimprove this. Taking into consideration patient and diagnostic variability, it would seem prudent todiscussmanagementcross-specialityinparticulardosingregimensfordrugsnottypicallyusedoutsideof the HIT arena. For the future it remains to be seen if the current trend to the increasing use ofLMWHs for dialysis will translate into a reduced incidence of HIT in chronic haemodialysis patients.Itisyettobeseen whattherapeuticrolethenew oralanticoagulantsmayplayinthisnichearea.

Managementofthrombocytopenia

The management of patients suspected of HIT begins at the time of consultation, often long beforeresultsoflaboratorytestingareavailable.Forpatientswithalowclinicalsuspicionof HIT, wedonotobtain testing and recommend continuation of heparin therapy. For patients with an intermediate orhighclinicalsuspicionofHIT,wediscontinueheparinandinitiateanalternativeanticoagulant.

Argatroban is the only nonheparin anticoagulant currently approved by the Food and DrugAdministration for the treatment of HIT, but other agents such as bivalirudin and fondaparinux areincreasingly used basedon successfulclinicalexperience.Dueto spacelimitations,wewillnotreview the pharmacology, dosing, and clinical experience of the nonheparin anticoagulants in HIT.The reader is referred to recent excellent comprehensive reviews on these topics.[1,36]The choice ofalternative anticoagulant is primarily driven by comorbidities and half-life considerations. We preferto use parenteral direct thrombin inhibitors (DTI) in the critically ill patient, often due to the need forprocedural interventions and/or underlying bleeding risk in these patients, in whom a shorter half-lifeis desirable. We recommend judicious use of these alternative anticoagulants due to high hemorrhagicpotential and lack of an antidote. If laboratory evaluation later reveals a low likelihood of HIT, wediscontinue alternative anticoagulants and resume heparin therapy. For patients with a laboratory-confirmed diagnosis of isolated HIT, we recommend ultrasound imaging of upper and lowerextremities to rule out subclinical thrombosis, because findings of thromboembolic complicationswould alter the duration of anticoagulation therapy. Once the patient is anticoagulated on analternative therapy and platelet

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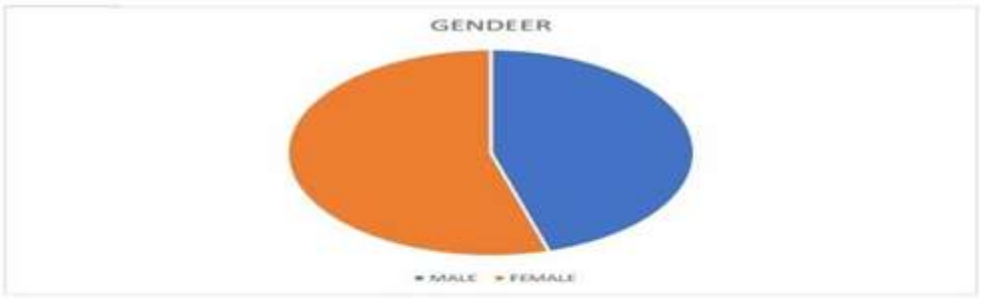
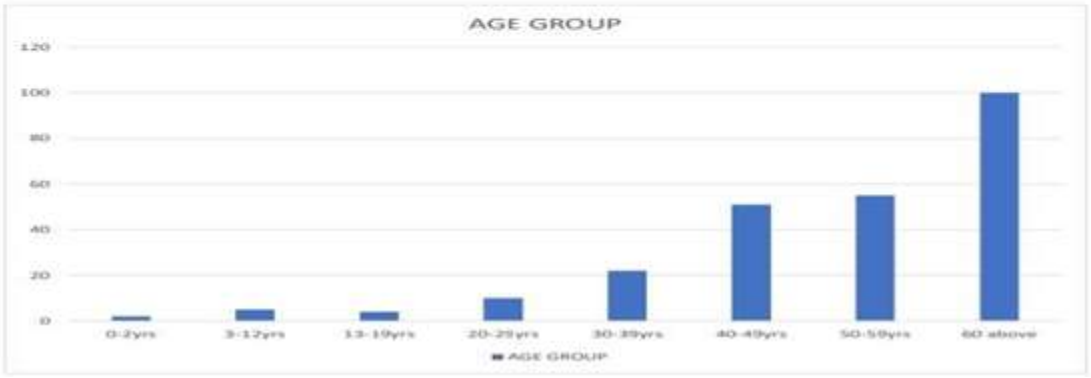
counts have increased back to baseline, we initiate warfarin therapy ata low dose (5 mg). Current guidelines recommend up to 4 weeks of anticoagulation with warfarin forpatients with isolated HIT and a minimum of 3 months for patients with HIT complicated bythrombosis.For patients with refractory or progressive thromboses on DTIs, we use plasmapheresiswith fresh-frozen plasma replacement as salvage therapy to reduce antibody burden.It should benotedthat theuseofplasmapheresis inHITis not acategorized indicationbytheAmericanSocietyofApheresis.

19. METHODOLOGY

Disease review study done by receiving the various method throughout the study period. Theliterature were collected from various sources. These literature are combined and the result of thestudyweretakenandthe discussionandconclusionwere made.StudyperiodstartsfromFebruarytoSeptember. Studysiteat Sree Krishna College of Pharmacy and Research Center .

II. RESULT





III. DISCUSSION

Heparininducedthrombocytopenia(HIT)isa severecomplicationthat canoccurinpatientsexposed to any form or amount of heparin products.A fall in platelet count and a hypercoagulablestate characterise HIT.Here we aim to access the potential complication of heparin inducedthrombocytopeniaandrecommendedtreatme ntof HIT.

Thecurrent studyrevealedthatfemalespatients(52%)weremoreth anMales(48%)andthemajorityofthe study population lies between the age group of 22 to 86 years.The mean age of patient with HITtype II was 62.4 years.According to the study ,it has been demonstrated that the prevalence of HITType II is less common in medical patients than surgical patients (0.7% vs 5%) and has a lowerincidencewithlow molecularweightheparinthan unfractionatedheparin(0.5%vs5%).

Thereviewbychangandparikhdemonstratei

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nbothgeneralanddialysispopulation,thefrequencyof HIT Type II is always significantly lower than the presence of HIAs.This Is supported by the work ofpalomo et al [12]who could find no significant relationship between the presence of HIA and eitherthrombocytopeniaorthrombosis.

To our knowledge there has only been one study aimed at determining the incidence of HIT type ll byyamamoto et al [7] found an incidence of 3.5% in 154 consecutive patients.increased incidence can beexplained by low threshold yamamoto et al had for screening for HIAs with indication such as clot indrip chamber or increased circuit pressure associated with 20% of drop in platelet count 28% of renalunithadcasesof HITtypellwithprevalencerateranging from0.22% to1.74%

Haemodialysispatients withHITtypellhadanaverageageof62 yrsandnosignificantdifferenceingender. The prevalence is considerably lower (0.26 per 100 patients)than previous estimates havesuggested and found that haemodialysis patient do not present in classical pattern with HIT type ll,asignificant proportion have delayed onset and only a minority have developed complications(17%).Anticoagulantbeingusedforthe sepatientsbutdanaparoidpredominates.

IV. CONCLUSION

Heparin induced thrombocytopenia remains a commonly encountered iatrogeniccomplications of heparin therapy in hospitalized patients. In the nearly 6 decades since theinitial description of the diseases, there have been major advances in understanding thepathogenesis of HIT, its varied clinical complications and treatment. Clinician treatingpatients with heparin should determine platelet count at baseline and hence forth at regularintervals beginningfromfifthdayoftherapy.Werecommendedc ommencementofwarfarintherapy concurrently with heparin infusion and discontinuation of heparin once warfarin hasbecome effective.

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