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Real World studies on undesirable effects of some Anti-Thrombotic Drugs in a tertiary Hospital

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Abstract

Introduction: Antithrombotic drugs include antiplatelet, anticoagulant and fibrinolytics. Antithrombotic drugs either block the formation of new clots, or prevent the growth of existing clots or reduce risk of complications from blood clots. These drugs are used in various Cardio and neurological diseases ranging from Angina, stroke to as Dual Antiplatelet Therapy (DAT) in post implantation of permanent medical devices. Antithrombotic drugs have numerous side effects from gastritis, prolonged bleeding, hemorrhage, tachycardia, tinnitus based on the class of drugs.

Study design and Objective: Though the undesirable effects of antithrombotic drugs are well established in controlled trails, there were rare studies in Real world population. Hence a prospective observational study was under taken to understand the undesirable effects in a Tertiary hospital in India and analyze the pattern based on age, gender, intended and indications of use and dosage regimen. The undesirable effects of Aspirin, Heparin and Clopidogrel were studied in 92 patients over a period of 6 months.

Results and Discussion: In the current study there were 8 cases were heparin was indicated and 50% of the patients complained of haemorrhage / bleeding and in 2 cases there is heavy bleeding during cut wounds. All this cases were found in patients where Heparin is used in Cardiology and neurological diseases and old age group on different indications of use. In 60 patients who are on Aspirin therapy 43 patients are in cardiology and 17 in neurological treatment. Most of the indications are for CAD, Myocardial Infraction (MI) and Angina. Important undesirable effects noted in the present study include SOB-9 patients, Tachycardia- 5, Blood in stools-4 patients, Tinnitus -3 patients and Ulcers in 3 patients. Of the 92 cases, Clopidogrel was prescribed for different indications of use in 24 patients. Of them 19 patients are in cardiology and 5 patients are in neurology treatment. Most commonly patients were diagnosed with MI, unstable angina and CVA Ischemic stroke, with observed undesirable effects like prolonged bleeding, dyspepsia, headache, indigestion, heart burn and tachycardia. The study clearly shows that prolonged bleeding was observed in 40% of the patients on clopidogrel mainly in segment with higher doses and on co-medication

Conclusion: The present study has shown similar undesirable effects evidenced in controlled clinical trials. However, the study indicates Intravenous administration of Heparin is advised than subcutaneous route and need for larger studies to substantiate the same. It is also recommended that patients on Aspirin should be recommended for low dose mainly in indications related to cardiovascular diseases than higher dosed. Most of the adverse effects are found in patients taking more than 75 mg and BID and TID. It could be related to dose induced effects and also the includes the age factor as most of them are geriatrics and not on anti-ulcer drugs. The study clearly shows that prolonged bleeding was observed in 40% of the patients on clopidogrel mainly in segment with higher doses and on co-medication. A case was reported on overdose of Clopidogrel which resulted in abnormalities in platelet aggregation that required emergency medical care.

Keywords: Antithrombotic Drugs, blood clot, Clopidogrel, Thromboembolic disease, Heparin Therapy

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1. Introduction

An antithrombotic agent is a drug that reduces the formation of blood clots i.e., thrombin. Antithrombotic drugs can be used therapeutically for prevention or treatment of a dangerous blood clot. The widespread use of antithrombotic drugs for the prevention and treatment of arterial and venous thrombosis. Thromboembolic disease continues to be a major cause of death and disability worldwide. This shows our inefficiency in searching efficacious and safe antithrombotic drugs. (1)

The term thrombosis means the formation of a thrombus, a type of blood clot. Thrombi can form on the wall of a blood vessel or in one of the chambers of the heart. When a thrombus obstructs blood flow to the heart or head, it can cause a heart attack or stroke. Antithrombotic drugs include antiplatelets, which prevent tiny discs that circulate in the blood, called platelets, from sticking to blood vessels, walls and to one another, and anticoagulants, which prevent blood from clotting.

The goals of antithrombotic therapy are to block the formation of new clots, prevent the growth of existing clots, and reduce a person's risk of complications from blood clots. To prevent blood clot formation or to reduce the risk of future vascular problems, antithrombotic medications are prescribed if a patient has blood clot or is at risk for having pulmonary embolism, heart attack or stroke.

Antithrombotics are indicated in Atrial fibrillation, Pulmonary hypertension, Cardiomyopathy, Pulmonary Embolism, Ischemic stroke, certain congenital heart disorders, Artificial valve replacement, Deep vein thrombosis, Unstable angina, Coronary artery bypass graft surgery, Angioplasty and stenting., Carotid artery disease, Peripheral arterial disease. (2)

Worldwide, Cardiovascular events represent the major cause of morbidity and mortality. A key role in the pathogenesis of these events is played by platelets. Antiplatelet medications are considered first-line therapy in preventing cardiovascular thrombotic events.

The major clinical indication for antiplatelet therapy has been the prevention of arterial thrombosis. Aspirin, the protype antiplatelet agent, has been in clinical use as an antithrombotic for almost a half a century. For several decades, antiplatelet therapy centered on the thromboxane pathway and its inhibition by aspirin, and aspirin remains the background template therapy for acute ischemic syndromes, as well as, secondary prevention. However, despite the wealth of data that support the use aspirin and indeed the data that suggest it should be more widely prescribed, aspirin remains a suboptimal antiplatelet agent.

Clopidogrel represents a major advance in antiplatelet therapy. In the CAPRIE trial, an 8.7% relative risk reduction in vascular death, ischemic stroke or myocardial infarction was found with clopidogrel versus aspirin. Although it is clear that clopidogrel is more effective than aspirin alone, dual antiplatelet pathway inhibition is more than additive in preventing thrombus formation. (3,4)

Prevention of stroke is a crucial health care issue, as stroke is the third cause of death and the first cause of major disability in developed countries. The established role of platelet aggregation in TIA or minor and major ischemic stroke has provided the rationale for many randomized trials of antiplatelet agents. The recent Antiplatelet Trials collaboration (APT) meta -analysis (1994) based on 142 trials involving 100,000 vascular patients confirmed the data of the previous overview (1998).

Aspirin, the only drug evaluated for primary prevention of ischemic events, is not indicated for safety reasons in subjects at low risk of occlusive disease. Compared to control, antiplatelet therapy, notably aspirin which is by far the most widely used agent in trials, provides a 27% risk reduction of stroke, myocardial infarction or vascular death in patients suffering from ischemic vascular events and a 22% risk reduction of these outcomes in patients having experienced a prior TIA/stroke. (5-7)

Cardiovascular disease, particularly coronary artery disease resulting from accelerated atherosclerosis, is the leading cause of morbidity and mortality in patients with diabetes mellitus. Of note, DM patients without a history of coronary artery disease have overall the same cardiac risk as non DM patients with a history of myocardial infarction(MI). Furthermore, patients with DM also have a higher risk of cardiovascular complications and recurrent athero-thrombotic events than non-DM patients.

The concomitant presence of cardiovascular risk factors and comorbidities that negatively effect of acute coronary syndrome(ACS), is higher in DM patients. The negative impact of DM on outcomes is maintained across the ACS spectrum, including unstable angina and non-ST elevation MI (NSTEMI).

Major adverse cardiovascular events including death, myocardial infarction, stroke and recurrent angina have all been shown to be significantly decreased when these agents are employed in the treatment of coronary atherosclerosis, acute coronary syndromes, myocardial infarction, and in the setting of percutaneous coronary intervention. As a growing number of patients on antiplatelet therapy are undergoing various surgical procedures, the potential risks and benefits these drugs will become increasingly important. Available data indicate that, when used appropriately, these drugs can be used safely prior to surgery. Efficacy in improving surgical outcomes and in preventing adverse cardiovascular events has been demonstrated. (8-10)

The most widely used antiplatelet agents include the information, coupled with emerging platelet monitoring techniques, may help additional assistance to assistance to the clinician to manage therapy and guide appropriate timing of both cardiac and non-cardiac surgery. Multiple studies have demonstrated the effectiveness of dual or triple antiplatelet therapy with aspirin, clopidogrel therapy in patients with acute coronary syndromes.

Treatment and prevention of numerous cardiovascular and neurological conditions are treated with antithrombotic drugs. The management which has to be given for different cardiological and neurological conditions is reviewed.

Concomitant to the thrombotic effect of these agents is increases in bleeding complications which can be fatal were considered in the study in order to provide the better health care. The possible undesirable effects that may occur while treating with these medications such as Aspirin, Clopidogrel, Heparin are discussed. The need of the study brought into light when the clinical observers

identified undesirable effects during the regular participation of ward rounds and while assisting patient complications by clinicians.

2. Study Design and Methodology:

In this study, the objectives were to assess the undesirable effects of Antithrombotics and to suggest better antithrombotic therapy. The study design is a prospective observational study which is conducted in INPATIENT facilities of the Department of Cardiology and Neurology. The study period is a 6 months with sample size of 92. The study subjects were selected from the Department of Cardiology and Neurology based on the following inclusion and exclusion criteria.

Inclusion criteria

- The patients admitted in the hospital with cardiovascular, neurological diseases.
- The age above 18 years.
- Patients of both genders.
- Patients with risk factors like Hypertension, Diabetes Mellitus, and Renal failure.
- Family history.
- Smokers and alcohol consumers.

Exclusion criteria

- Patients below 18 years of age.
- Patients with history of pre-eclampsia.

We conducted a prospective observational study in the Inpatient Departments of cardiology and neurology, Care Hospitals, Hyderabad, India from month of November 2021 to May 2022 (six months). After getting approval from the Institution Human Ethics Committee (IHEC), we have recruited 92 patients under the guidance of physician based on inclusion and exclusion criteria.

Materials used to carry out the study process were:

1. Patient consent form.

2. Data collection form.

3. Patient information leaflet.

Patient consent form

It is used for the convenience of the patient.it was prepared in three different languages -Telugu, Hindi, English. The patients were given complete information about the study and upon their acceptance; they were recruited after signing the patient consent form

Patient data collection form

The following data was collected from the recruited patients using a suitable data collection from designed under the guidance of physician.

a. Demographic details include name, age, gender, and date of admission, date of discharge for the identification of the patient. Socioeconomic data such as an address and locality.

b. Chief complaints and diagnosis to identify the disease condition of the patient.

c. Present medication history was used to know further details of the disease.

d. Vitals to know the patient's condition.

Patient information leaflet

Patient information leaflets were given to patients during counselling sessions which provides brief information on proper diet during the treatment with aspirin, clopidogrel, and heparin and to overcome the serious adverse events. The patients were counselled on their condition and detailed the information in the leaflet for a better understanding of the patient.

3. Results and Discussion

Data of 92 patients were collected from Cardiology and Neurology Departments. The data includes the patients Age, Gender, Diagnosis, intended use, Indications of use, dose of antithrombotic, Dosage regimen (Duration / frequency), route of administration and most importantly the Undesirable effects which include the side effects, adverse events and serious adverse events.

Harm or Damage to the patient and Risk, probable the harm to happen, and, happening, Side-effects to patients-Clinical (usually) effects that may happen due to the use of a drug, but are not related to the intended use are quite important to review the safety profile of the drug

Undesirable side-effects - Side effects for which the risk is considered unacceptable (depending on the acceptability criteria, disorientation might be unacceptable)

4. Heparin Therapy

a. Bleeding complications: All the adverse effects of heparins are related to their wide variety of biological activities, with bleeding being the most important safety issue, resulting directly from the potency of heparin as an anticoagulant. However, it is hard to define the bleeding risk, since it depends on numerous parameters including the indication, dosage, method, and duration of heparin application, the clinical study design and definition of bleeding as well as patient characteristics and determinants of bleeding such as type of surgery and co-medication.

b. Nonbleeding complications: Heparins are caused by binding of heparin molecules to proteins other than anti thrombin and to cells, which is generally more pronounced with unfractionated heparin than with low-molecular-weight heparins. Accordingly, heparin-induced thrombocytopenia, the most severe nonbleeding adverse reaction, occurs about 10 times less with low-molecular-weight heparins than with unfractionated heparin. Frequent and therefore important adverse reactions of heparins are skin lesions resulting from delayed-type hypersensitivity reactions. All the other undesirable effects are discussed as well, but they are mostly clinically irrelevant.

Less common side effects include Abdominal or stomach pain or swelling back pain or backaches

bleeding from the gums when brushing teeth, blood in the urine, constipation, coughing up blood dizziness, headaches, severe or continuing, heavy bleeding or oozing from cuts or wounds, joint pain, stiffness, or swelling. menstrual bleeding, unexpected or unusually heavy. unexplained bruising or purplish areas on the skin. unexplained nosebleeds. vomiting of blood or material that looks like coffee grounds

Rare effects include, Blood under the skin (blood blister) at the place of injection, chest pain chills or fever, fast or irregular breathing, irritation, pain, redness, or ulcers at the place of injection itching and burning feeling, especially on the bottom of the feet, nausea or vomiting numbness or tingling in the hands or feet, pain, coldness, or blue color of the skin on the arms or legs. peeling of the skin. puffiness or swelling of the eyelids or around the eyes shortness of breath. skin color change, especially near the place of injection or in the fingers, toes, arms, or legs. skin rash, hives, or itching. tearing of the eyes. tightness in the chest. trouble with breathing. wheezing

In earlier clinical studies the undesirable effects that applies to heparin: injectable kit, injectable solution, intravenous solution. (11-13)

a. **General:** The most common adverse reaction was hemorrhage.

b. **Cardiovascular:** Post marketing reports: Hemorrhage, retroperitoneal hemorrhage

c. **Hematologic:** Very common (10% or more): Thrombocytopenia (up to 30%), Frequency not reported: Plasma lipoprotein lipase increased, Post marketing reports: Heparin resistance, Hypersensitivity, Frequency not reported: Conjunctivitis, cyanosis, tachypnea, feeling of oppression, antineurotic edema, anaphylactic shock. Post marketing reports: Chills, fever, urticaria, asthma, rhinitis, lacrimation, headache, nausea, vomiting, anaphylactic reactions, shock, itching, burning

d. **Local:** Frequency not reported: Erythematous nodules, infiltrated and sometimes eczema-like plaques Post marketing reports: Local irritation, erythema, mild pain, hematoma, ulceration, histamine-like reactions, skin necrosis

e. **Immunologic:** Frequency not reported: Allergic reactions, hyper eosinophilia, Post marketing reports: Heparin-induced thrombocytopenia, heparin-induced thrombocytopenia and thrombosis, generalized hypersensitivity reactions

f. **Endocrine:** Frequency not reported: Hypoaldosteronism, Post marketing reports: Adrenal hemorrhage, acute adrenal insufficiency, fatal adrenal hemorrhage, aldosterone synthesis suppressed

g. **Metabolic:** Frequency not reported: Plasma potassium increased, hyperkalemia, metabolic acidosis, Post marketing reports: Rebound hyperlipidemia

h. **Musculoskeletal:** Frequency not reported: Significant bone demineralization, spontaneous bone fracture, Post marketing reports: Osteoporosis

i. **Dermatologic:** Frequency not reported: Ecchymosis, Post marketing reports: Cutaneous necrosis, delayed transient alopecia

j. **Hepatic:** Frequency not reported: Serum transaminases increased, Post marketing reports: ALT elevated significantly, AST elevated significantly

In the current study there were 8 cases were 50% of the patients complained of haemorrhage / bleed in and in 2 cases there is heavy bleeding during cut wounds. All this cases were found in patients where Heparin is used in Cardiology and neurological diseases and old age group on different indications of use.

Apparently there is one case where the patient taking Heparin, 40mg, Subcutaneously, twice a day complained of chest pain. However, on further trail investigation it was noted that the patient is also taking Aspirin as co-medication and its related to gastric ulcers and not related to heparin linked undesirable effects.

Though the patient group is small it was quite evident the common undesirable effects of bleeding to heavy bleeding are noted in the patients in line with the previous reported literature.

5. Clopidogrel Therapy

The undesirable effects apply to clopidogrel: Oral tablet, (14)

a. **General:** The most commonly reported adverse effect was bleeding, including life threatening and fatal bleeding.

b. **Hematologic:** Uncommon (0.1% to 1%): Fatal bleeding, eosinophilia, leucopenia, increased bleeding time, thrombocytopenia, Rare (0.01% to 0.1%): Neutropenia, Very rare (less than 0.01%): Decreased platelet count, Post marketing reports: Serious cases of bleeding (mainly skin), hemarthrosis, hematoma, hemorrhage of operative wound, fatal hemorrhage (intracranial, gastrointestinal, and retroperitoneal), thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A, aplastic anemia, pancytopenia, agranulocytosis, granulocytopenia, anemia.

In the COMMIT study (n=45,852), the incidence of major non-cerebral or cerebral bleeding was 0.6% in clopidogrel plus aspirin treated patients, with 0.4% classified as major non-cerebral (0.2% fatal) and 0.2% as hemorrhagic stroke (0.2% fatal).

Non-major noncerebral bleeding or any noncerebral bleeding occurred in 3.6% and 3.9% of patients receiving this drug plus aspirin, respectively. Major bleeds were defined as cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

Table 1. Segregated data of Patients on Heparin

S. No.	Patient Name/ Case No.	Intended Use	Age	Gender	Diagnosis	Drug	Drug Dosage	Route of Administratio	Frequency	Anti-platelet	Anticoagulant	Indications	Undesirable Effects
1	CD00204	Cardiology	59	M	Coronary Artery Disease	Heparin	5000IU	IV	OD	-	✓	Prevention And Treatment Of Thrombotic Event	Heavy Bleeding Or Woozing From Cuts Or Wounds.
2	CD00206	Cardiology	64	M	Coronary Artery Disease	Clexane	40mg	SC	BD	-	✓	Reducing Serious Cardiac Ischemic Events	Chest Pain
3	CD00213	Cardiology	48	M	AF With CVR	Heparin	5000IU	IV	BD	-	✓	To Reduce The Risk Of Thrombus Formation	
4	NL00230	Neurology	56	F	CVA	Heparin	5000IU	IV	OD	-	✓	Prevention Of Thrombus Propagation	Haemorrhage
5	NL00251	Neurology	65	M	CVA	Heparin	5000IU	IV	OD	-	✓	Prevention Of Thrombus Propagation	Haemorrhage
6	CD00259	Cardiology	59	M	Coronary Artery Disease	Heparin	5000IU	IV	OD	-	✓	Prevention And Treatment Of Thrombotic Event	Bleeding
7	CD00286	Cardiology	60	M	CVA	Heparin	5000IU	IV	OD	-	✓	Prevention Of Thrombus Propagation	Haemorrhage
8	CD00261	Cardiology	47	M	Coronary Artery Disease	Clexane	40mg	SC	BD	-	✓	Reducing Serious Cardiac Ischemic Events	Woozing From Cuts Or Wounds.

Table 2. Segregated data of patients on Clopidogrel

S. No.	Patient Name/ Case No.	Intended Use	Age	Gender	Diagnosis	Drug	Drug Dosage	Route of Administration	Frequency	Anti-platelet	Anticoagulant	Indications	Undesirable Effects
1	CD00205	Cardiology	70/Y	F	LVF	Clopidogrel	75mg	PO	BD	✓	-	Reduce The Incidence Of Stroke	Indigestion, Heart Burn
2	CD00209	Cardiology	67/Y	F	Coronary Artery Disease	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Incidence Of Stroke	Prolonged Bleeding
3	CD00217	Cardiology	35/Y	M	TIA	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Headache
4	CD00219	Cardiology	60/Y	F	CVA Ischemic Stroke	Clopidogrel	75mg	PO	TID	✓	-	Reduce The Rate Of Recurrent Stroke	Vomiting's
5	CD00220	Cardiology	50/Y	M	ACS-NSTEMI	Clopidogrel	300mg	PO	OD	✓	-	Reduce The Risk Of Major Ischemic Events	Dyspepsia

6	CD00228	Cardiology	67/Y	M	CVA	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Dizziness, Headache
7	CD00233	Cardiology	72/Y	F	AFI,CVA	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Stomach Pain ,Excessive Tiredness
8	NL00236	Neurology	58/Y	M	Brain Stroke	Clopidogrel	150mg	PO	BD	✓	-	Reduce The Rate Of Recurrent Stroke	Bleeding More Easily Than Normal
9	CD00244	Cardiology	70/Y	M	Myocardial Infarction	Clopidogrel	75mg	PO	BD	✓	-	Reduction Of Adverse Ischemic Incidence	Prolonged Bleeding
10	CD00247	Cardiology	47/Y	F	Unstable Angina	Clopidogrel	75mg	PO	BD	✓	-	Reduction Of Adverse Ischemic Incidence	Gum Bleed
11	CD00250	Cardiology	56/Y	M	Myocardial Infarction	Clopidogrel	75mg	PO	OD	✓	-	Reduction Of Adverse Ischemic Incidence	Diarrhoea
12	CD00253	Cardiology	51/Y	F	Unstable Angina	Clopidogrel	75mg	PO	OD	✓	-	To Prevent Recurrent Ischemic Event	Headache, Vomiting's
13	NL00255	Neurology	82/Y	M	Stroke	Clopidogrel	150mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Bleeding
14	CD00260	Cardiology	63/Y	F	LVF	Clopidogrel	75mg	PO	BD	✓	-	Reduce The Incidence Of Stroke	Indigestion, Heartburn
15	CD00264	Cardiology	47/Y	F	Coronary Artery Disease	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Incidence Of Stroke	Epistasis
16	CD00266	Cardiology	60/Y	F	CVA Ischemic Stroke	Clopidogrel	75mg	PO	TID	✓	-	Reduce The Rate Of Recurrent Stroke	Nose Bleed, Gum Bleed
17	CD00267	Cardiology	50/Y	M	ACS-NSTEMI	Clopidogrel	300mg	PO	OD	✓	-	Reduce The Risk Of Major Ischemic Events	Bronchitis
18	CD00275	Cardiology	67/Y	M	CVA	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Dizziness, Headache
19	CD00279	Cardiology	70/Y	M	Myocardial Infarction	Clopidogrel	75mg	PO	BD	✓	-	Reduction Of Adverse Ischemic Incidence	Prolonged Bleeding
20	CD00282	Cardiology	47/Y	F	Unstable Angina	Clopidogrel	75mg	PO	BD	✓	-	Reduction Of Adverse Ischemic Incidence	Gum Bleed, Tachycardia
21	CD00285	Cardiology	76/Y	M	Myocardial Infarction	Clopidogrel	75mg	PO	OD	✓	-	Reduction Of Adverse Ischemic Incidence	Prolonged Bleeding
22	NE00288	Cardiology	51/Y	F	Unstable Angina	Clopidogrel	75mg	PO	OD	✓	-	To Prevent Recurrent Ischemic Event	Gum Bleed, Tachycardia
23	CD00290	Cardiology	35/Y	M	TIA	Clopidogrel	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Headache
24	CD00292	Cardiology	40/Y	F	CVA Ischemic Stroke	Clopidogrel	75mg	PO	TID	✓	-	Reduce The Rate Of Recurrent Stroke	Nose Bleed, Gum Bleed

Table 3. Segregated data of Patients on Aspirin

S. No.	Patient Name/ Case No.	Intended Use	Age	Gender	Diagnosis	Drug	Drug Dosage	Route of Administration	Frequency	Anti-platelet	Anticoagulant	Indications	Undesirable Effects
1.	CD00200	Cardiology	60/Y	M	Angina	Aspirin	80mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	Hallucinations
2.	CD00201	Cardiology	72/Y	F	Pericardial Effusion	Aspirin	75mg	PO	OD	✓	-	Reduce Inflammation And Relief Pain	
3.	CD00203	Cardiology	59/Y	M	Angina	Aspirin	75mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	Difficulty In Breathing, Hallucinations
4.	CD00207	Cardiology	81Y	F	Coronary Artery Disease	Aspirin	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Diarrhoea, Skin Rash
5.	NL00208	Neurology	64/Y	M	CAD	Aspirin	75mg	PO	TID	✓	-	Reduce The Incidence Of Stroke	Abdominal Pain, Diarrhoea
6.	CD00210	Cardiology	66/Y	F	IWMI	Aspirin	75mg	PO	OD	✓	-	It Helps To Slow The Formation Of The Clots	SOB, Loss Of Hearing
7.	CD00211	Cardiology	60/Y	M	AWMI	Aspirin	75mg	PO	OD	✓	-	It Helps To Slow The Formation Of The Clots	Swelling Of The Eyes
8.	CD00212	Cardiology	49/Y	M	LVF	Aspirin	75mg	PO	OD	✓	-	Improve Blood Flow	Tachycardia
9.	NL00214	Neurology	65/Y	F	NSTEMI Accelerated HTN	Aspirin	75mg	PO	OD	✓	-	Reducing The Blood Clots	Tachycardia, Heart Burn
10.	NL00215	Neurology	82/Y	F	Amoebic Dysentery	Aspirin	75mg	PO	OD	✓	-		Blood In Stools
11.	CD00216	Neurology	40/Y	M	CVA	Aspirin	150mg	PO	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	Ringing In Ears
12.	CD00218	Cardiology	60/Y	M	Angina Pectoris	Aspirin	75mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	Nausea, Heart Burn
13.	CD00221	Cardiology	24/Y	M	RHD With Severe AR	Aspirin	75mg	PO	OD	✓	-	Helps To Slow The Formation Of Clots	Swelling Of The Eyes
14.	CD00222	Cardiology	47/Y	M	Cad With AWMI	Aspirin	325mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Nausea
15.	CD00223	Cardiology	46/Y	F	Cad With IWMI	Aspirin	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	SOB
16.	CD00224	Cardiology	49/Y	M	RHD,DCMP, LVD	Aspirin	150mg	PO	OD	✓	-	Helps To Slow The Formation Of Clots	Fast Breathing, Allergic Reaction
17.	CD00225	Cardiology	60/Y	F	Post PTCA	Aspirin	75mg	PO	OD	✓	-	To Reduce The Risk Of Heart Attack And Ischemic Stroke	Liver Damage, Increase In Bilirubin
18.	CD00226	Cardiology	21/Y	M	LVH	Aspirin	75mg	PO	OD	✓	-	Helps To Prevent Blood Clots Forming In Artery	Stomach Pain
19.	CD00227	Cardiology	32/Y	F	LVH	Aspirin	75mg	PO	OD	✓	-	Helps To Prevent Blood Clots Forming In Artery	Nausea, Stomach Pain

20.	CD00229	Cardiology	82/Y	F	Coronary Artery Disease	Aspirin	75mg	PO	OD	✓	-	Reduce The Incidence Of Stroke	Drowsiness
21.	CD00231	Cardiology	35/Y	M	Acute Ischemic Stroke	Aspirin	150mg	PO	OD	✓	-	May Prevent New Clots From Forming And Hence Improve Recovery After Stroke	Increase In Heart Beat
22.	NL00232	Neurology	47/Y	F	CVA	Aspirin	75mg	PO	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	SOB, Blood In Stools
23.	CD00234	Cardiology	77/Y	M	CHF	Aspirin	75mg	PO	OD	✓	-	Aspirin Thins The Blood Which Helps Prevent Blood Clot From Forming	Sweating, Increasing Heart Beat
24.	NL00235	Neurology	80/Y	F	CVA	Aspirin	75mg	PO	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	Burning In Throat, SOB
25.	NL00237	Neurology	82/M	M	Meningioma Decreased Evaluation	Aspirin	150mg	PO	OD	✓	-	Reduces The Risk Of New Infarction	Confusions, Blur Vision
26.	NL00238	Neurology	82/M	M	Generalized Tonic-Clonic Seizures	Aspirin	75mg	PO	OD	✓	-	Reduces The Frequency And Duration Of Spontaneous Recurrent Seizures	Double Vision
27.	NL00239	Neurology	80/F	F	Cerebrovascular Accident	Aspirin	75mg	PO	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	Nausea, Drowsiness
28.	NL00240	Neurology	55/Y	F	Vertigo Decreased Evaluation	Aspirin	75mg	PO	OD	✓	-	Potential Efficiency In Preventing Recurrent Migraine Headache	Blurred Vision,
29.	CD00241	Cardiology	58/Y	M	Angina Pectoris	Aspirin	75mg	PO	OD	✓	-	Decrease Recurrent Of Cardiovascular Events	SOB
30.	CD00242	Neurology	74/Y	F	Parkinsonism	Aspirin	75mg	PO	OD	✓	-	Upregulate Tyrosine Hydroxylase And Increases Dopamine Production In Dopaminergic Neuron	Confusion, Nausea
31.	CD00256	Cardiology	60/Y	M	Angina	Aspirin	80mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	SOB, Tachycardia
32.	CD00257	Cardiology	72/Y	F	Pericardial Effusion	Aspirin	75mg	PO	OD	✓	-	Reduce Inflammation And Relief Pain	
33.	CD00258	Cardiology	38/Y	M	Angina	Aspirin	75mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	SOB
34.	CD00262	Cardiology	50/Y	F	Coronary Artery Disease	Aspirin	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Ulcers, Headache
35.	CD00263	Cardiology	54/Y	M	Cad	Aspirin	75mg	PO	TID	✓	-	Reduce The Incidence Of Stroke	GI Bleeding, Headache
36.	CD00265	Cardiology	47/Y	M	Angina Pectoris	Aspirin	75mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	Swelling Of Face, Blurred Speech
37.	CD00268	Cardiology	24/Y	M	RHD With Severe AR	Aspirin	75mg	PO	OD	✓	-	Helps To Slow The Formation Of Clots	GI Bleeding
38.	CD00269	Cardiology	47/Y	M	CAD With AWMI	Aspirin	325mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Nausea
39.	CD00270	Neurology	56/Y	F	CAD With IWMI	Aspirin	75mg	PO	OD	✓	-	Reduce The Rate Of Recurrent Stroke	Nausea, SOB
40.	CD00271	Neurology	39/Y	M	RHD,DCMP,LVD	Aspirin	150mg	PO	OD	✓	-	Helps To Slow The Formation Of Clots	Decreased Urination, Ringing In Ear

41.	CD00272	Neurology	30/Y	F	Post PTCA	Aspirin	75mg	PO	OD	✓	-	To Reduce The Risk Of Heart Attack And Ischemic Stroke	Allergic Reactions, Raised Hypertension
42.	CD00273	Cardiology	21/Y	M	LVH	Aspirin	75mg	PO	OD	✓	-	Helps To Prevent Blood Clots Forming In Artery	Nausea
43.	CD00274	Cardiology	32/Y	F	LVH	Aspirin	75mg	PO	OD	✓	-	Helps To Prevent Blood Clots Forming In Artery	Swelling Of Eyes, Face Tongue
44.	CD00276	Cardiology	72/Y	F	Coronary Artery Disease	Aspirin	75mg	PO	OD	✓	-	Reduce The Incidence Of Stroke	Blood In Stools
45.	CD00277	Cardiology	74/Y	F	Parkinsonism	Aspirin	75mg	PO	OD	✓	-	Upregulate Thyrosine Hydroxylase And Increases Dopamine Production In Dopaminergic Neuron	Confusion
46.	CD00291	Cardiology	47/Y	M	Angina Pectoris	Aspirin	75mg	PO	OD	✓	-	Reduce The Ability Of Blood Clot	Tachycardia
47.	CD00243	Cardiology	60/Y	M	Myocardial Infarction	Aspirin	150mg	PO	OD	✓	-	Reduces The Blood Clots That Are Blocking Arteries	Fast Breathing, Dehydration
48.	CD00245	Cardiology	67/Y	F	Angina Pectoris	Aspirin	80mg	PO	OD	✓	-	Decrease Recurrent Of Cardiovascular Events	Sweating
49.	CD00246	Cardiology	69/Y	M	Ischemic Heart Disease	Aspirin	150mg	PO	OD	✓	-	Helps Prevent Blood Clots Forming In Arteries And Lower Risk Of Stroke	Peptic Ulcer, Vomiting
50.	NL00248	Neurology	65/Y	M	Cerebrovascular Accident	Aspirin	150mg	PO	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	GI Bleeding
51.	NL00249	Neurology	55/Y	M	Cerebrovascular Accident	Aspirin	75mg	PO.	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	SOB
52.	NL00252	Neurology	55/y	F	Parkinsonism	Aspirin	75mg	PO	OD	✓	-	Upregulate Thyrosine Hydroxylase And Increases Dopamine Production In Dopaminergic Neuron	Loss Of Hearing, Ringing In Ear
53.	CD00254	Cardiology	66/Y	M	Myocardial Infarction	Aspirin	150mg	PO	OD	✓	-	It Helps To Slow The Formation Of The Clots	GI Bleeding
54.	CD00278	Cardiology	60/Y	M	Myocardial Infarction	Aspirin	150mg	PO	OD	✓	-	Reduces The Blood Clots That Are Blocking Arteries	Thrombocytopenia
55.	CD00280	Cardiology	67/Y	F	Angina Pectoris	Aspirin	80mg	PO	OD	✓	-	Decrease Recurrent Of Cardiovascular Events	GI Bleeding
56.	CD00281	Cardiology	69/Y	M	Ischemic Heart Disease	Aspirin	150mg	PO	OD	✓	-	Helps Prevent Blood Clots Forming In Arteries And Lower Risk Of Stroke	Tachycardia
57.	CD00283	Cardiology	65/Y	M	Cerebrovascular Accident	Aspirin	150mg	PO	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	GI Bleeding
58.	CD00284	Cardiology	45/Y	M	Cerebrovascular Accident	Aspirin	75mg	PO.	OD	✓	-	Reduces The Tendency Of The Platelets In The Blood To Clump	Peptic Ulcer, Blood In Stools
59.	CD00287	Cardiology	55/y	F	Parkinsonism	Aspirin	75mg	PO	OD	✓	-	Upregulate Thyrosine Hydroxylase And Increases Dopamine Production In Dopaminergic Neuron	Haemorrhage
60.	CD00288	Cardiology	66/Y	M	Myocardial Infarction	Aspirin	150mg	PO	OD	✓	-	It Helps To Slow The Formation Of The Clots	Tachycardia

In the CURE study (n=12,562), the incidence of fatal bleeding (0.2%) and intracranial hemorrhage (0.1%) was the same between clopidogrel with aspirin and placebo with aspirin groups.

c. **Gastrointestinal:** Common (1% to 10%): Abdominal pain, gastrointestinal hemorrhage, dyspepsia, diarrhea, nausea, gastritis, Uncommon (0.1% to 1%): Vomiting, flatulence, constipation, gastric, peptic, or duodenal ulcer, Rare (0.01% to 0.1%): Retroperitoneal hemorrhage, Post marketing reports: Colitis (ulcerative or lymphocytic), pancreatitis, stomatitis, In the CAPRIE study (n=19,185), gastrointestinal hemorrhage occurred in 2% of patients taking clopidogrel compared to 2.7% taking aspirin. Bleeding requiring hospitalization occurred in 0.7% clopidogrel-treated and 1.1% aspirin-treated patients.

d. **Hypersensitivity:** Post marketing reports: Angioedema, anaphylactic reactions, cross reactive hypersensitivity among thienopyridines (e.g. ticlopidine, prasugrel), hypersensitivity reactions

e. **Cardiovascular:** Common (1% to 10%): Chest pain, hypertension, angina pectoris, coronary artery disorder, peripheral ischemia, Very rare (less than 0.01%): Hematoma, Post marketing reports: Hypotension, syncope, vasculitis

f. **Nervous system:** Common (1% to 10%): Dizziness, headache, Uncommon (0.1% to 1%): Paresthesia, Rare (0.01% to 0.1%): Vertigo, intracranial hemorrhage, Post marketing reports: Taste disturbances, ageusia

g. **Musculoskeletal:** Common (1% to 10%): Arthralgia, back pain, Post marketing reports: Arthritis, myalgia, musculoskeletal bleeding

h. **Psychiatric:** Common (1% to 10%): Depression, Post marketing reports: Hallucinations, confusion

From the sample size of 92 cases we segregated data of 24 patients who are using clopidogrel. Among them 12 are male and 12 are female patients. 4.The average age of the patients which is noted as 57years. Most commonly patients were diagnosed with MI, unstable angina and CVA Ischemic stroke with observed undesirable effects like prolonged bleeding, dyspepsia, headache, indigestion, heart burn and tachycardia.

Of them 19 patients are in cardiology and 5 patients are in neurology Among them 12 are male and 12 are female patients. 4.The average age of the patients which is noted as 57years. Most commonly patients were diagnosed with MI, unstable angina and CVA Ischemic stroke. with observed undesirable effects like prolonged bleeding, dyspepsia, headache, indigestion, heart burn and tachycardia.

The undesirable effects include indigestion in 2 patients, Heartburn in 2, Prolonged bleeding in 11. Vomiting in 6, Dyspepsia in 2, Dizziness in 1, Headache in 6. Stomach-ache in 1, Tiredness in 1. The study clearly shows that prolonged bleeding was observed in 40% of the patients on clopidogrel mainly in segment with higher doses and on co-medication. Case study on Clopidogrel overdose – Platelet Aggregation

Here we report a case study in our Study project of a 47-year-old male, with a known medical history of type 2 diabetes mellitus, anterior myocardial infarction, and stent implantation to left circumflex coronary artery, was surgically treated for a left middle cerebral artery aneurysm, 3 months previously. The patient, who had no history of hemorrhagic dyscrasia, was brought to the Emergency Department within 1 hour of ingesting 3 tablets of Plavix† (1650 mg clopidogrel) at time, On physical examination, blood pressure and pulse rate were 120/80 mmHg and 68 beats/min, respectively. There was no bleeding, petechia or ecchymoses. On complete blood count examination, platelet count was 195 000/mm3, hemoglobin was 14.1 g/dL, hematocrit was 41%, and leukocyte count was 6200/ mm3

Liver enzyme levels were within normal limits. Prothrombin time was 12 s, and activated thromboplastin time was 22.5 s. Gastric decontamination was carried out, but no tablets were recovered and activated charcoal was given. On follow-up of patient, no prolongation of coagulation tests, no decrease in platelet counts, no changes in complete blood counts or on blood smears were observed. No neurologic deficit or change in liver function tests was detected.

Platelet aggregation was examined by dual channel optical platelet aggregator. Aggregation with 10 mm/mL collagen, 1.5 mm/mL ristocetine, 10 mm/mL adrenaline and 10 mm/mL ADP were examined. First measurement, performed on day 1 (2 hours after the exposure), revealed ADP and adrenaline-induced aggregation fractions as 9 and 29%, respectively, with normal response to collagen (106%) and ristocetine (83%) On day 3, aggregation fractions for ADP and adrenaline were 15 and 34%, respectively, and on day 7 after platelet rich plasma infusion (5 U) were applied, the same fractions were found as 30 and 70%, respectively. As bleeding risk was deemed acceptable with aggregation over 30%,6 the patient was transferred to a psychiatric clinic for treatment of major depression. (15)

There is little information on overdose of clopidogrel. In animal studies, a lethal single oral dose of clopidogrel for mice and rats were 1500 and 2000 mg/kg, respectively. Lethal single oral dose for baboons was higher at 3000 mg/kg clopidogrel. Symptoms and signs of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage. There was one case of overdose with clopidogrel, a 34-year-old female who took a single 1050 mg (14 tablets per 75 mg) clopidogrel with no untoward effect, and recovered without event.3 No adverse events were reported after a single oral dose of 600 mg (equivalent to eight standard 75 mg tablets) clopidogrel in healthy volunteers. The bleeding time was prolonged 70%, which was similar to that typically observed with the therapeutic dose of 75 mg of clopidogrel (Plavix†) per day.5

Abnormalities of platelet aggregation improved in association with treatment of a platelet transfusion. The role of platelet transfusion in patients with platelet

aggregation abnormalities after overdose of clopidogrel is unknown. Hence overdose of clopidogrel may lead to abnormalities in platelet aggregation.

6. Aspirin Therapy

More frequently reported side effects include: dyspepsia, epigastric discomfort, heartburn, and nausea. Along with its needed effects, aspirin may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention. (16)

Some side effects of aspirin may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medical condition. Common side effects include Acid or sour stomach, anxiety. Belching. Dizziness. dry mouth. Hyperventilation. Irritability. Shaking. stomach discomfort, upset, or pain. trouble sleeping. unusual drowsiness, dullness, tiredness, weakness, or feeling of sluggishness

The following undesirable effects applies to aspirin: compounding powder, oral capsule, oral capsule extended release, oral delayed release capsule, oral delayed release tablet, oral gum, oral powder for reconstitution, oral tablet, oral tablet chewable, oral tablet disintegrating, oral tablet dispersible, oral tablet extended release, rectal suppository

a. **Gastrointestinal:** Common (1% to 10%): Dyspepsia, Frequency not reported: GI bleeding, ulceration, perforation, nausea, vomiting, pancreatitis, gastric irritation, GI erosions, gastritis, melena, hematemesis, gingival bleeding

b. **Renal:** Frequency not reported: Interstitial nephritis, papillary necrosis, renal insufficiency and failure

c. **Hematologic:** Common (1% to 10%): Increased bleeding tendencies, Rare (0.01% to 0.1%): Aplastic anemia agranulocytosis, thrombocytopenia, Frequency not reported: Prolongation of prothrombin time, disseminated intravascular coagulation, coagulopathy, antepartum and postpartum bleeding, anemia

d. **Hypersensitivity:** Rare (0.01% to 0.1%): Anaphylactic reactions including shock, Frequency not reported: Urticaria, angioedema, skin rashes

e. **Dermatologic:** Uncommon (0.1% to 1%): Urticaria. Rare (0.01% to 0.1%): Steven-Johnson syndrome, Lyell's syndrome, erythema nodosum, erythema multiforme, Frequency not reported: Purpura, hives

f. **Hepatic:** Frequency not reported: Transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, hepatic insufficiency

g. **Metabolic:** Frequency not reported: Thirst, dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis, hypoglycemia, hyperglycemia, hyperuricemia, salt and water retention

h. **Cardiovascular:** Rare (0.01% to 0.1%): Hemorrhagic vasculitis, Frequency not reported: Dysrhythmias, hypotension, tachycardia

i. **Nervous system:** Frequency not reported: Cerebral edema, coma headache, subdural or intracranial hemorrhage, seizures, lethargy, dizziness

From the sample size of 92 cases we have segregated data of 60 patients who are using aspirin. Among them 35 are male and 25 female patients. 3.The average age of patient which was noted as 57years. Most commonly patients was diagnosed with CAD, CVA, angina, MI, LVH, with observed undesirable effects like SOB, tachycardia, GI bleeding, nausea, blood in stools, and ulcers.

In the current study 60 patients are on Aspirin. 43 patients are in cardiology and 17 in neurological treatment. Most of the indications are for CAD, Myocardial Infraction (MI) and Angina.

Undesirable effects noted in the present study include Hallucinations- 2 patients, SOB-9 patients, Tracycardia-9 patients, Abdominal pain-1 patients, Diarrhea-1 patient, Heartburn-2 patients , Blood in stools-4 patients, Blurred vision-2 patients, Confusion-2 patients, Swelling of eyes-2 patients, GI bleeding-6 patients, Ringing ears-3 patients, Allergic reactions-1 patient, Nausea-6 patients, Liver damage increased bilirubin levels-1 patients, Increased blood pressure-1 patient, Hemorrhage-1 patient,Thrombocytopenia-1 patient, Ulcers-3 patients, Decreased urination-1 patient

Most of the adverse effects are found in patients taking more than 75 mg and more than once a day. It could be related to dose induced effects and also includes the age factor as most of them are geriatrics and not on anti-ulcer drugs, a co-medication advised while on Aspirin therapy.

7. Conclusions

In the current study there were 8 cases were 50% of the patients complained of haemorrhage / bleed in and in 2 cases there is heavy bleeding during cut wounds. All this cases were found in patients where Heparin is used in Cardiology and neurological diseases and old age group on different indications of use. Apparently there is one case where the patient taking Heparin, 40mg, Subcutaneously, twice a day complained of chest pain. However, on further trail investigation it was noted that the patient is also taking Aspirin as co-medication and its related to gastric ulcers and not related to heparin linked undesirable effects. Though the patient group is small it was quite evident the common undesirable effects of bleeding to heavy bleeding are noted in the patients in line with the previous reported literature. Intravenous administration of Heparin is advised than subcutaneous route and need for larger studies to substantiate the same

Important undesirable effects noted in the present study ion Patients in Aspirin therapy include SOB-9 patients, Tachycardia- Blood in stools-4 patients, Ringing ears-3 patients Ulcers-3 patients. It is advised from the current study that anti- ulcer drugs should be made mandatory for the patients on Aspirin based on the undesirable reports It is also recommended that patients on Aspirin should be recommended for low dose Aspirin mainly in indications of use related to cardiovascular diseases than higher dosed Most of the adverse effects are found in

patients taking more than 75 mg and more than once a day. It could be related to dose induced effects and also the includes the age factor as most of them are geriatrics and not on anti-ulcer drugs, a co-medication advised while on Aspirin therapy

Most commonly patients were diagnosed with MI, unstable angina and CVA Ischemic stroke in Clopidogrel group. with observed undesirable effects like prolonged bleeding, dyspepsia, headache, indigestion, heart burn and tachycardia. The undesirable effects include Prolonged bleeding in 11. Vomiting in 6, Dyspepsia in 2, Headache in 6. The study clearly shows that prolonged bleeding was observed in 40% of the patients on clopidogrel mainly in segment with higher doses and on co-medication. A case study was reported on overdose of Clopidogrel which resulted in abnormalities in platelet aggregation that required emergency medical care

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article

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