JOURNAL Of Medical Science And Clinical Research
IGM Publication   An Official Publication Of IGM Publication

Role of Antiplatelet Drugs in Deep Vein Thrombosis

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Abstract
Background: *Acute and chronic venous diseases are the most prevalent medical conditions worldwide. Acute venous thromboembolism is a serious and frequently lethal disease, whereas chronic venous insufficiency can be the source of discomfort, disability and loss of working days. Deep vein thrombosis and its further complications are very well known. Despite the best possible management, morbidity and mortality cannot be prevented in all.*
Material and Methods: *The study was conducted in the department of Cardiovascular and Thoracic Surgery of a super-specialty hospital. All the patients admitted in the department, referred from or examined in other departments, and attended in our outpatient department, irrespective of age, sex, disease, and who followed the department for at least one year were included in the study. Vascular doppler of the affected limb was the investigation of choice. Acenocaumarol, aspirin were the commonly used anticoagulant and antiplatelet drugs*
Results: *13.66% of the patients never came for follow up, 12.94% were managed by other departments, 58.82% were from the inpatient and 41.17 from the outpatient department. Pain and edema limb were the most common symptoms. Vascular doppler helped confirming diagnosis in all. Parenteral anticoagulants during the early course of treatment, simultaneous addition of oral anticoagulant drugs, were the first line of treatment. Oral anticoagulants combined with antiplatelet drugs was the commonly used combination in majority of the patients.*
Conclusion: *Antiplatelet added right from the inception for first few weeks, and during follow-up, especially in patients at high risk, those who can't effort low molecular weight heparin, those who don't get blood tests regularly and in those who can't effort regular follow up. Low dose antiplatelet drugs help in decreasing progression of the disease and decrease morbidity and mortality.*
Keywords: *Deep vein thrombosis, Acenocaumarol, Aspirin, Clopidogrel.*

Introduction

Deep Vein Thrombosis (DVT) is one of the most common problem all over the world, and pulmonary embolism is the most feared complication of DVT, which if massive, outcome is dismal even in the best equipped medical centers. Porcine intestinal mucosa extract, heparin, is the commonly used parenteral anticoagulant

immediately after the diagnosis is made. Heparin binds to antithrombin and accelerates the rate at which it inhibits various coagulation proteases. However, despite the best possible therapeutic measurement by activated partial thromboplastin time (aPTT), therapy may not be adequate, and if the ideal therapeutic level of anticoagulation is not reached in first 24 hours, the risk of recurrence of thromboembolism increases. The anticoagulant effect of heparin disappears within hours after discontinuation of the drug, aPTT monitoring facilities are not available everywhere, besides heparin can cause bleeding, even in patients whose aPTT is within therapeutic range, in addition heparin induces thrombocytopenia, more in surgical patients, which may further complicate venous thromboembolism and arterial thrombosis. Though there is no substitute to heparin the overall outcome because of heavy dose, continuous monitoring, patient related factors, and other complications is not always promising. The alternative to heparin is, derivatives of heparin which include low-molecular-weight-heparins (LMWH) and fondaparinux. These heparin derivatives differ in source, molecular weight, target, renal excretion, antidote effect. Besides being expensive, LMWH and fondaparinux have little effect on platelets which is the hall mark of clot formation, and the other complications are same as that of heparin. Oral anticoagulants such as warfarin and nicoumalone though ideal anticoagulants, start their effect after 2 to 3 days and at times the therapeutic effect may not be achieved up to weeks, also the bleeding complications are high with heavy doses, besides all the patients do not tolerate these drugs. Under such circumstances it is mandatory to start low dose antiplatelet drugs simultaneously, these drugs achieve the therapeutic levels immediately, and at least prevent the further aggregation of platelets, progression of the disease, and can be continued without the danger of severe side effects. Low dose, 75 milligram (mg) of antiplatelet drugs help prevent the progression of the disease, decrease the bleeding complications

associated with heavy doses of anticoagulants, and act as bridge till an acceptable INR is achieved with the effects of anticoagulants, also these drugs do not need the monitoring of INR and aPTT. Aspirin and clopidogrel are the acceptable antiplatelet drugs, in combination their effects are additive, or even synergistic and have been used in the present study in combination though in low doses. Heavy doses of aspirin 324 mg to 4 gm are needed for other problems, but for antiplatelet action, and preferably in combination 75 milligrams is sufficient. Also, patients are happy taking a drug which neither needs regular blood testing nor follow up.

The progression of DVT, is compounded by limb edema, sepsis, systemic manifestation, and deteriorating general wellbeing, which further worsens if the patient has associated arterial pathology. Only parenteral and oral anticoagulants which have various limitations and side effects are not sufficient in the initial stages of management of these patients.

Materials and Methods

The study was conducted in the department of Cardiovascular and Thoracic Surgery, in a Super-Specialty Hospital. All the patients admitted in the department, referred from or examined in other departments, and attended in our outpatient department, irrespective of age, sex, disease, and who followed the department for at least one year were included in the study. Patients who were taking warfarin for DVT, those who were shifted to other departments and those who did not come for regular follow-up were not included in the study. A detailed history, thorough general and systemic examination was contemplated in all. Besides Doppler and routine investigations, specific tests were performed as per the requirement of each patient. Symptomatic treatment as and when needed in the form of antibiotics, analgesics, care of the limb, and management of the causative pathology was given. In patients with edema and without any bleeding, trypsin / chymotrypsin combination was

given for six days. Majority of the patients were diagnosed and managed on outdoor patient basis, Patients with clinical features of DVT were started on LMWH, till the Doppler report was available, when the other drugs were started. Depending on the weight and underlying disease, majority were started on LMWH, very few were given heparin, oral anticoagulants were started preferably simultaneously, except in those who could not take orals. Besides acenocaumarol, single antiplatelet drug was used in majority, followed by oral anticoagulant and double antiplatelet therapy. The antiplatelet drugs were continued if the patient did not tolerate oral anticoagulants, or could not effort regular INR tests, or till the patient had achieved desired INR at least on three occasions or six weeks of overall treatment. Antiplatelet after the diagnosis of DVT were also given for three to six months in patients who stopped anticoagulants because of one or the other reason. The course of the disease was observed in patients receiving only anticoagulants and those receiving antiplatelet in addition. Commonly used anticoagulant and antiplatelet drugs were: -

Heparin- given by continuous intravenous infusion, intermittent infusion every 4 to 6 hours, or subcutaneous injections every 8 to 12 hours. The therapy was started with 5000 unit's stat followed by 800-1600 units per hour, therapy was monitored by aPTT.

LMWH - which in effect are anticoagulants, have little effect on platelets. The usual dose was .4 to .6 ml daily or twice daily, by subcutaneous route.

Acenocaumarol- a vitamin K antagonist, was the oral anticoagulant used.

Aspirin - causes inactivation of cyclooxygenase enzyme which is required for prostaglandin and thromboxane synthesis, was used in a dose of 75mg daily.

Clopidogrel- inhibits adenosine diphosphate from binding to its receptors on platelets, also blocks the body's production of clotting substances, the daily dose used was 75 mg. Anticoagulants were continued for at least 6 to 12 months, and antiplatelet were also given for 1 to 3 months, but

in patients where acenocaumoral could not be given, antiplatelet were given for more time. Besides in patients managed on outdoor basis, antiplatelet were added to patients who had more severe disease, other comorbidities, or were at high risk of thromboembolic episodes, were bed ridden, and where the INR and aPTT estimation facilities were either not available, or not affordable, or refused by the patients. In some patients who had continuous swelling, pain and could not get regular INR done, drugs were continued for a year. All the patients were followed up in outpatient department, detailed examination was conducted, and after three months of treatment, if patient had improved clinically, Doppler studies were done to see for dissolution of thrombus, in partial recanalization or persistence of thrombus the drugs were continued for six months, and then the tests repeated. Effect of anticoagulants and antiplatelet was assessed by clinical history / examination and Doppler studies. Partial and complete recanalization was assessed at 3, 6 and 12 months of follow up. With a follow up of 6 to 12 months, except for some, treatment was only stopped if patient had no clinical evidence of DVT, and venous Doppler studies were normal. At follow up long term manifestation of pain, edema, hyperpigmentation, secondary varicose veins, complete occlusion of venous lumen, additional thrombotic occlusions and ulceration were observed. Morbidity and mortality was recorded.

Results

Of the 139 patients only 102 were included in the study, 13.66% patients never came for follow up and 12.94% patients had to be managed by other departments. 58.82% patients were from the outpatient, and 41.17% from the inpatient department. Pain and edema legs were the common symptoms, Table 1. Some were under the treatment of orthopedic surgeons, other allopathic doctors and quacks. 22.54% patients had features of chronic venous insufficiency, secondary varicose veins, pigmentation and ulcers

at the time of presentation. Vascular Doppler was suggestive of DVT in all, majority in lower limb and extensive, both legs in 6.86%, upper limb in 13.72%, multiple limbs in 5.88%, and associated active arterial disease in 6.86% patients. Combination of acenocaumarol and aspirin was used in 67.64% of the patients, Table-2.

Titrating therapeutic range of INR took a minimum of 1 to 3 weeks, some patients did not take the drugs regularly, and majority did not follow the guidelines for optimization of oral anticoagulation with emphasis on INR. Patients on antiplatelet drugs had no major complication, investigations were rarely required, defaulters of oral anticoagulants were better suited, dose of oral anticoagulant was less, and even if the patient had a lower INR, there was no adverse outcome.

Results of treatment at six months follow up were better in patients receiving antiplatelet in addition to oral anticoagulant, even patients receiving only dual antiplatelet had good outcome. Clinical and Doppler evidence of secondary varicosity was noted in 38.23% of the patients, but the rate of recanalization despite the best possible treatment was not encouraging. At follow up, partial recanalization at 3 months was observed in 16.66%, at 6 months recanalization was documented by Doppler studies in 38.23% and at 12 months recanalization was 84.31% in oral anticoagulant and combination group. Complete recanalization was not documented in any patient before 6 months. It was observed that majority of the patients hadn't done INR for months together, and those who had done, hadn't maintained therapeutic INR, either they did not have the facility available at their nearest health center, or were not taking anticoagulants regularly. A detailed history revealed that majority 40.10% had stopped oral anticoagulants after the acute symptoms of DVT were over, pain and edema had subsided, or feared bleeding complications. 50% were literally only on dual antiplatelet therapy, since they had stopped oral anticoagulant after symptomatic relief, or after three months of treatment. Patients with multiple limb thrombosis

had adverse outcome. Bleeding episodes were recorded in 13.72%, majority in triple drug therapy, of these the anticoagulation dose was reduced in 50.00%, stopped in 28.57%, aspirin was stopped in 21.42%. At follow up long term manifestation of pain, edema, hyperpigmentation, secondary varicose veins, complete occlusion of venous lumen, additional thrombotic occlusions, and ulcerations were equal in patients in both the groups. The mortality was 6.86%, and was observed more in inpatient groups, with disseminated disease, other co morbidities, malignancy, and admission for bleeding complications.

Table-1 Showing symptoms and clinical signs in patients with DVT at presentation*

Type of Symptom/Sign	Number of Patients	Percentage
Pain Limb	102	100
Edema limb	91	89.21
Painful movements	79	79.45
Fever	63	67.76
Pigmentation	48	47.05
Ulcers	17	16.66
Breathlessness	16	15.68

*More than one symptom / sign was present in a patient

Table 2 Showing anticoagulant and antiplatelet used

Drug used	Number of patients	Percentage
Heparin	04	3.92
LMWH	47	46.07
Acenocaumarol	88	86.27
Dual Therapy*	69	67.64
Tripple Therapy**	23	22.54
Dual antiplatelet***	10	9.80

*Anticoagulant with aspirin, **anticoagulant with aspirin and clopidogrel, ***Only dual antiplatelet therapy

Comments

Venous thrombi were once regarded as relatively static structures that changed little over time, but, it is now clear that venous thrombi undergo a dynamic evolution beginning soon after their formation, and the venous lumen is most often reestablished after a thrombotic event. Pulmonary embolism with its attendant mortality is the most devastating complication of DVT, and inadequate treatment of proximal lower extremity thrombosis is associated with 20 to 50% risk of clinically significant recurrent thromboembolism,[1] with approximately 90% of thromboemboli arising

from lower extremity veins.[2] Symptomatic pulmonary embolism may also complicate up to 17% of proximal upper extremity thrombi.[3] Also as many as 29 to 79% of patients, may have long term manifestation of pain, edema, hyperpigmentation and ulceration after an episode of acute DVT, also called as post thrombotic syndrome (PTS).[4] The risk of thromboembolism while taking warfarin is 1-2% per year. With the addition of aspirin to therapy with warfarin, a further 77% reduction in the risk of thromboembolism is achieved.[5] Tripple antithrombotic therapy such as oral anticoagulant with aspirin and clopidogrel is well known,[6] though the benefits may not be always so, [7] also irrespective of the drug combination used, the overall long term prognosis of warfarin treated patients has been disappointing.[8] In the acquired risk factors for thrombosis, besides others there is more activation of platelets (they become spherical, develop pseudopodia, secrete the contents of storage granules and adhere to each other) and activation of coagulation system in sepsis. [9] Despite the best possible evaluation, the cause of thrombosis and even at times spontaneous emboli remains un identified. [10] DVT which effects about 1-2% of population with annual incidence of 1 in 500,[11] with nearly one quarter developing PTS within one year of episode of thrombosis.[12] Anticoagulants though prevent propagation and extension, have little effect on thrombi, which resolve naturally through a process of organization and vein recannalization.[13] Rapid resolution of thrombus is associated with less valvular damage, reduced venous hypertension and few post thrombotic complications. [14] Thrombolysis and mechanical removal increase morbidity, hemorrhage and re-thrombosis,[15] necessitating the better understanding of thrombi formation. Venous thrombi arise in both the vein valve pockets and dilated sinuses of lower limbs, are fibrin and red cell rich, they have laminar structure consisting of layers of platelets, leucocytes and fibrin that encompasses the main erythrocyte mass, this is unlike the

amorphous structure of a blood clot, which consists predominantly of erythrocytes within a fine fibrin mesh,[13] exposure of the collagen rich wall is said to lead to platelet aggregation and further leucocyte sequestration which results in a nidus for thrombus propagation.[16] Inflammation is considered an important mechanism for venous thrombus formation, supplemented by increase of inflammatory marker, C-reactive protein in patients having DVT.[17] Some good additions in the management of DVT are, catheter directed thrombectomy, percutaneous mechanical thrombectomy, but their indications are few, are available at very few centers and the patients can develop severe peri-and postprocedural complications such as intracranial, retroperitoneal, musculoskeletal, genitourinary and gastrointestinal bleed.[15] Newer drugs such as Dabigatran, Rivaroxaban, Apixaban and Endoxaban are promising but are not without major complications.

Despite the best possible anticoagulant, the chances of platelet aggregation and further thrombo-emboli formation is not abolished in these patients, further the laboratory tests are not available to everyone, patients are reluctant for a drug which needs regular monitoring, and the PTS is seen in more than 50% despite the anticoagulants. Aspirin and clopidogrel are prescribed for their antiplatelet action, and the former has well established role in arterial blood vessel disease even with a dose of 75 mg, clopidogrel is commonly prescribed in perioperative period by the orthopedic surgeon, the only advantage may be, that, emergency surgery can be performed even without stopping these drugs, though the fact is that, it is better to stop these drugs 5 to 7 days before surgery. The Scottish intercollegiate guidelines recommend stopping clopidogrel 7 days before surgery.[18] The management approach in present study is not in similarity to other studies.[19] However, almost 50% of the patients being managed with dual antiplatelet therapy contrasts with other studies. The reason being patients had stopped taking oral

anticoagulant drugs after the acute symptoms subsided, or after three months. There were no major complications in patients on dual antiplatelet therapy when compared to patients on dual antiplatelet / anticoagulation therapy at follow up and in doppler studies. Dual antiplatelet therapy for prevention and treatment of venous thromboembolism was used with good results in the present study, the role of aspirin in preventing the recurrence, and treatment of venous thromboembolism is well established.[20-22] Aspirin is recommended for prevention and treatment of both arterial and venous thromboembolism.[23]

Antiplatelet drugs were more useful in patients with major risk factor for thromboembolic episodes, associated arterial / cardiac pathology, bed ridden, major illness or where heavy doses of anticoagulant could not be given. The mortality being less in the present study cannot be taken as significant, in view of the fact that majority of the patients were managed from outpatient department.

Conclusion

DVT can present with a grim phenomenon, preventive measures help decrease the incidence, clinical suspicion/radiological evaluation confirms the diagnosis. Injectable and oral anticoagulation drugs are the treatment of choice. In high risk group, some antiplatelet drugs should also be added, If the patient cannot take oral anticoagulants for one or the other reason, dual antiplatelet therapy should be given till recanalization occurs or for at least three to six months. Pharmacotherapy is not without complications.

Limitations

The study has limitations, in that, the duration of symptoms and drug treatment of those patients who had presented with complications of DVT was not known. It could not be established how long did they have the symptoms, what was the initial presentation, what was the natural course of the disease without treatment. Also, majority of the patients were not following the advice strictly, and it cannot be said with certainty when had they actually stopped the anticoagulation drugs.

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