RIFAMPICIN CONTAINING ATT REGIMEN AS AN EMERGING CAUSE OF THROMBOEMBOLIC COMPLICATIONS

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ABSTRACT

BACKGROUND

In India, most of the anti-tuberculosis regimens under Revised National Tuberculosis Control Programme (RNTCP) are rifampicin based. Venous Thrombosis (VT) is a rare side effect of rifampicin and very few cases are reported worldwide. Studies have demonstrated possible association between VT and use of rifampicin, in patients treated with rifampicin containing regimens.

MATERIALS AND METHODS

This was an observational study done in New Medical College Hospital, Kota during the period June 2016 to July 2018. Careful watch was kept on patients who were admitted for any complications after initiation of ATT.

RESULTS

During this period, 4 patients, who were taking ATT, presented with thromboembolic events. Mean time of presentation was 71±22 days after starting ATT. 3 patients had lower limb DVT & 1 patient had pulmonary artery thrombus.

CONCLUSION

Though venous thrombosis is uncommon side effect of rifampicin, treating physicians should be cautious during treatment.

KEYWORDS

Tuberculosis, Rifampicin, Venous Thrombosis.

HOW TO CITE THIS ARTICLE: Saluja M, Swami YK, Chittora S, et al. Rifampicin containing ATT regimen as an emerging cause of thromboembolic complications. J. Evid. Based Med. Healthc. 2018; 5(45), 3164-3167. DOI: 10.18410/jebmh/2018/644

BACKGROUND

Tuberculosis is most prevalent infectious diseases worldwide as well as in India. According to WHO TB statistic 2015, globally incidence of TB was 9.6 million and in India it was 2.2 million.[1]

Thrombosis is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system. When a blood vessel is injured, the body uses platelets and fibrin to form a blood clot to prevent blood loss. Even when blood vessel is not injured, blood clots may form in the body under certain conditions. Rifampicin, contribute to the hypercoagulable state by decreasing production and increasing clearance of anticoagulant hepatic proteins.[2] Rifampicin can also cause endothelial injury which favours thrombosis.[3] Very few cases are reported worldwide.[4] In our case, after ruling out other hypercoagulable states, association between rifampicin and VT is established and improvement of patient indicates the role of physician in recognizing and treating the condition at early phase.

Financial or Other, Competing Interest: None.
Submission 06-10-2018, Peer Review 10-10-2018,
Acceptance 17-10-2018, Published 03-11-2018.
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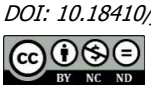
DOI: 10.18410/jebmh/2018/644



Aim of the Study

To find out whether rifampicin causes any thromboembolic complications in patients who are on rifampicin containing ATT.

MATERIALS AND METHODS

This was an observational study, done at New Medical College Hospital, Kota during period of June 2016 to July 2018. Watchful observation was done of patients who were on ATT and admitted for any complication during therapy.

Inclusion Criteria

1. Patients on anti-tubercular treatment (ATT) for any tubercular aetiology.
2. Admitted during treatment period for any complication suspecting as thrombotic event.

Exclusion Criteria

1. Patients admitted within 1 month of starting ATT.
2. Recent history of major surgery
3. Prolonged immobilisation
4. Known case of valvular heart disease
5. Previous history of thromboembolic event

RESULTS

During whole period various complications were noted, of which 4 patients presented with some form of thromboembolic complication.

Case 1

A 33-year-old male presented with painful swelling in the left leg for last 3 days. Patient was taking Anti Tubercular Treatment (ATT) under RNTCP in weight adjusted dosing which included isoniazid, rifampicin, pyrazinamide, ethambutol for last 2 months for tubercular pleural effusion. He had no history of recent surgeries, no prolonged immobilisation & no history of similar complaints in past.

On examination left leg was swollen, erythematous with increased local temperature and tenderness. Cardiovascular and pulmonary examination was essentially normal.

Case 2

A 26-year-old male presented with difficulty in breathing, generalised swelling (mainly in lower limbs), decreased weight and appetite for last 20 days. Patient was diagnosed pulmonary tuberculosis 45 days back and since then was taking ATT under RNTCP which includes isoniazid, rifampicin, pyrazinamide, ethambutol.

On examination patient was thin and lean, lower limb swelling was present. Patient was cyanosed on admission. Abdomen was distended with moderate hepatomegaly and shifting dullness. On admission BP (120/70 mm of Hg), pulse (120/min) and oxygen saturation was 50% without oxygen. On chest auscultation bilateral air entry was decreased (more so in right side) with bilateral crepitations and bilateral apical bronchial breath sounds.

Ultrasonography abdomen shows significant ascites, moderate hepatomegaly. Ascitic fluid was transudative in nature.

X-ray chest PA view showed old tubercular lesions.

Case 3

A 40 years old male presented with inguinal pain, swelling, redness and pain in right leg since 4-5 days. He was on ATT for last 3 months for sputum positive pulmonary TB. ATT contained rifampicin, isoniazid, pyrazinamide, ethambutol for 2 months followed by isoniazid, rifampicin & ethambutol since last 1 month. He had no history of recent surgery, prolonged immobilisation & previous similar event.

On examination right leg was swollen, erythematous with increased local temperature and tenderness. Cardiovascular and pulmonary examination was essentially normal.

On USG abdomen, there was no evidence of any intra-abdominal malignancy or abdominal lymphadenopathy.

Case 4

A 38 years old male presented with swelling, redness and pain in left leg up to knee joint since last 3-4 days. He was taking ATT for pleural effusion for last 3 months. ATT consist of rifampicin, isoniazid, pyrazinamide, ethambutol for 2 months followed by isoniazid, rifampicin & ethambutol since last 1 month. He had no history of recent surgery, prolonged immobilisation & previous similar event.

On examination left leg was swollen, erythematous with increased local temperature and tenderness. Cardiovascular and pulmonary examination was essentially normal.

Intra-abdominal malignancy & lymphadenopathy was ruled out by USG abdomen.

Laboratory findings: Routine laboratory investigations including CBC, liver function test, renal function test, blood sugar, lipid profile, HIV, HBsAg and anti HCV, were done in all cases, which are shown in table 3.

All hypercoagulable states were ruled out i.e. protein C, protein S, antiphospholipid antibody, serum homocysteine level, serum fibrinogen level, Coomb's test, rheumatoid factor. Ultrasonography abdomen was done in all patients to rule out intra-abdominal causes of lower limb DVT i.e. abdominal malignancy or lymphadenopathy. (Table 3)

Radiological study reports (colour doppler or CT scan) are shown in table 2.

Parameters	Case 1	Case 2	Case 3	Case 4
Age (years)/sex	33/male	26/male	40/male	38/male
Site of TB	Pleural effusion	Pulmonary TB	Pulmonary TB	Pleural effusion
Time of presentation after initiating ATT	45 days	60 days	90 days	90 days
History of previous thromboembolic events	no	no	No	No

Table 1. Comparison of Cases on the Basis of Different Parameters

Case	Site of Thromboembolic Event	Colour Doppler / CT Scan Findings
Case 1	Left leg	Thrombus starting from left popliteal vein involving femoral, common femoral extending till left iliac vein
Case 2	Pulmonary artery	Acute right pulmonary artery thromboembolism with pulmonary artery hypertension -bronchiectatic changes in right upper lung and fibrocalcific opacities in entire right and left upper lobe suggestive of old tuberculosis
Case 3	Right leg	Right leg popliteal & femoral vein thrombus
Case 4	Left leg	Left posterior tibial and popliteal vein thrombus

Table 2. Site of Thromboembolic Complication

Parameter	Case 1	Case 2	Case 3	Case 4
Haemoglobin	15	12.5	12.7	13.3
TLC	7440	8430	7690	9600
Platelet count	154000	358000	254000	178000
Renal function	Normal	Normal	Normal	Normal
Liver function	Normal	Normal	Normal	Normal
HIV/HBsAg/Anti HCV	Negative	Negative	Negative	Negative
Serum homocysteine	Normal	Normal	Normal	Normal
Plasma fibrinogen levels	Normal	Normal	Normal	Normal
Direct Coombs tests	Negative	Negative	Negative	Negative
Rheumatoid factor	Negative	Negative	Negative	Negative
Protein C and S	Normal	Normal	Normal	Normal
Antiphospholipid antibody	Negative	Negative	Negative	Negative
Proteinuria	Present	Present	No	No
Lipid profile	Normal	Normal	Normal	Normal

Table 3. Comparative Laboratory Finding of Cases

Management

Along with continuation of ATT, patients were treated with low molecular weight heparin and warfarin for thrombus. Warfarin dose was titrated to achieve target INR of 2-3. Within some days of hospital stay patients responded favourably with improvement in constitutional symptoms. Patients were discharged and advised to continue ATT, warfarin and regular follow up.

DISCUSSION

Tuberculosis (TB) remains one of the vulnerable communicable diseases in the world. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease.[5] Rifampicin is one of first line drugs for tuberculosis treatment. It acts by inhibiting bacterial DNA dependant RNA polymerase. Rifampicin is effective liver enzyme inducer promoting up regulation of hepatic cytochrome p450 enzymes (CYP2C9, CYP3A4), increasing the rate of metabolism of other drugs that are cleared by liver through this enzyme.[6] Frequently, a higher dose of warfarin is necessary to achieve therapeutic INR levels, because of rifampicin effects on cytochrome P450.[7] Commonly encountered side effects with rifampicin are jaundice, raised LFTs (14%), GIT symptoms (1-2%), flu like symptoms, pruritus, rash (1-5%). Thrombosis is uncommon side effect seen with rifampicin. This does not contraindicate the use of this drug in patients at risk, but patients with risk factors should be supervised.

Immunoallergic reaction which is induced by rifampicin may activate the coagulation process and initiate the DIC. Rifampicin as an antigen binds to platelets and erythrocytes to form immune complexes. Activated complement may cause platelet and, erythrocyte injury, and vascular endothelium impairment.[8] Because of this mechanism small blood clot formation occurs in the vessels which can cause VTE.

However, tuberculosis itself is a pro coagulant state because of hypercoagulability, venous stasis and endothelial dysfunction. Other responsible factors may be higher levels of fibrinogen, fibrin degradation products, tissue plasminogen activator and inhibitor. Decreased anti-thrombin III and reactive thrombocytosis may also cause VTE. Hypercoagulability can also occur by increased clearance or decreased production of anticoagulant proteins.[9,10] But in such cases patient usually presents with thrombotic events at the time of diagnosis of TB. Altered haemostatic changes which put TB itself as pro coagulant state, normalise during first month of disease. All cases in this study was presented after 45 days of starting ATT.

According to study by Patel SR et al, in 2017, there is an emerging concern that VTE could also result from drugs which form a component of ATT. This probable association between rifampicin and DVT stated above does not contraindicate use of this drug.[11]

According to a study by Supriya Sarkar, Kaushik Saha et al, in 2012, there were isolated reports of DIC due to anti-tubercular drugs, probably rifampicin.[12] Studies also demonstrated a possible association between DVT and the use of rifampicin with a relative risk of 4.74 in patients treated with rifampicin containing regimens.[3] According to same study occurrence of DVT in the third week in a case of tubercular pleural effusion when effusion was improving both clinically and radiologically might suggest other than tubercular aetiology for DVT. DVT resolution when rifampicin was withdrawn from the regime might indicate that the drug was the perpetrator.[13]

In a study on 2096 people using rifampicin, 49 (2.34%) patients are found to have DVT as side effect. In this study group, DVT was found especially in males (89.36%), old age more than 60 years (59.57%).[14,15] FDA research report states that percentage of Rifampicin taking patients, where DVT is reported as side effect is 0.5385%.[14]

CONCLUSION

Though venous thrombosis is uncommon side effect of rifampicin, treating physicians should be cautious during initial phase of treatment. Rifampicin should be continued along with initiation of anticoagulants.

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