

Assessment of the Anticoagulant Effect of Curcumin as Adjuvant Therapy to Enoxaparin in Covid-19 Iraqi Patients

Anticoagulant
Effect of
Curcumin in
Covid-19

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ABSTRACT

Objective: To assess the anticoagulant effect of curcumin as adjuvant treatment to enoxaparin in COVID-19 patients.

Study Design: Randomized open-labelled controlled trial study.

Place and Duration of Study: This study was conducted at the College of Pharmacy, Al-Esraa University, Baghdad, Iraq from 1st February 2020 to 31st July 2020.

Methods: Fifty-eight patients with confirmed Covid19 were enrolled into 2 groups: Group A; 29 patients were given Enoxaparin prophylactic dose 4000 IU twice daily every 12 hrs. Group B; 29 patients were given Enoxaparin prophylactic dose 4000 IU twice daily every 12 hrs + Curcumin 500 mg 3 times daily.

Results: A significantly higher level of improvement in the outcomes of D-dimer serum level in the group treated with enoxaparin and curcumin in comparison with group A which was treated with enoxaparin alone ($P < 0.05$).

Conclusion: The overall results of this clinical study showed a significant D-dimer reduction by curcumin supplementation as well as reducing mortality and enhancing the overall clinical outcome of the treatment when used as an adjunct to enoxaparin.

Key Words: Curcumin, D-dimer, Enoxaparin, COVID-19, Anticoagulant effect

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INTRODUCTION

Coronavirus disease-19 (COVID-19), a severe respiratory illness caused by SARS-associated coronavirus-2 (SARS-CoV-2). The "(SARS-CoV-2)" is a single-stranded RNA coronavirus that enters the human cell mainly by binding to angiotensin-converting enzyme 2 (ACE 2)^{1,2}, which in general ranges from asymptomatic or mild symptoms including fever, headache, cough, fatigue, dyspnea, diarrhea, and myalgia to even fatal cases.^{3,4}

Even though the respiratory compromise is the main feature of the disease that elevated circulating D-dimer levels which is a by product of the degradation of fibrin found in blood after blood clot fibrinolysis plays a mechanistic role in thrombo-inflammation in Covid 19

which's also associated with mortality, suggesting a distinct coagulation disorder related to COVID-19.^{5,6}

Curcumin is a polyphenol derived from the Curcuma long a plant and has been used extensively in complementary and alternative medicine, as it is non-toxic and safe with various therapeutic properties. Modern scientific research has demonstrated its anti-inflammatory, antioxidant, anti-carcinogenic, antithrombotic and cardiovascular protective effects.^{7,8}

METHODS

A randomized open-labelled controlled trial was carried out to assess the effect of adding curcumin to enoxaparin in patients with COVID-19. A total of 58 patients aged (19-75) with confirmed Covid were enrolled in this study. All patients are eligible to study if they were fulfilling the criteria of diagnosis COVID-19 and had a PCR test positive as well as symptomatic and radiologic evidence of mild to moderate COVID-19. Study follow-up was for about 5 to 10 days. Eligible patients were randomly allocated into two groups as follows: Group A; 29 patients given Enoxaparin prophylactic dose 4000 IU twice daily every 12 hrs Group B; 29 patients given Enoxaparin prophylactic dose 4000 IU twice daily every 12 hrs + Curcumin 500 mg 3 times daily Patients were recommended to take Enoxaparin injection SC twice daily while curcumin 500mg cap three times daily after meal clinical

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outcomes were evaluated by measuring D-dimer serum levels. The data was entered and analyzed through SPSS-25.

RESULTS

The non-significant statistical differences between both groups concerning gender and age ($P>0.05$) [Fig. 1]. The change in serum D-dimer level was statistically non-significant between groups neither at baseline nor after treatment. However, a significantly higher level of improvement in the outcomes of D-dimer serum level was seen in group B compared to that in group A after treatment ($P<0.05$). A non-significant change in D-dimer serum levels was demonstrated after treatment with enoxaparin alone compared to baseline levels, as a matter of fact, there was a slight increase in D-dimer serum level after treatment with enoxaparin alone ($P>0.05$) (Table 1).

Table No.1: Comparison of D-dimer in pre- and post-treatment in both groups

D-dimer	Group A (Enoxaparin)	Group B (Enoxaparin + curcumin)	P-value
Pre-treatment	1.6783	2.8341	0.574
Post-treatment	1.8248	1.3369	0.257

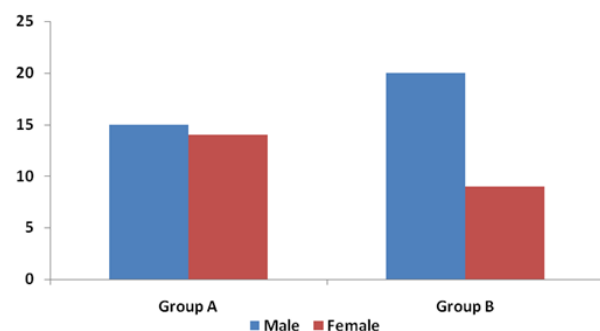


Figure No. 1: Comparison of genders in both groups

DISCUSSION

Coronavirus disease 2019 (COVID-19) is associated with extreme inflammatory response, disordered hemostasis, and high thrombotic risk. D-dimer is a fibrin breakdown product that has a mechanistic role in COVID-19 thrombo-inflammation. As a result, it might be considered a global marker of hemostasis activation in COVID-19.^{9,10} Recent autopsy studies supported this hypothesis of COVID-19 patients the fibrin thrombi observed in enlarged capillaries and small blood vessels, as well as widespread extracellular fibrin deposition.^{11,12} The hypercoagulable condition and secondary hyperfibrinolysis in vivo that result in coagulopathies during COVID-19 infection can be explained by two different hypotheses. One is the

increased levels of pro-inflammatory cytokines (IL-6, IL-1, and TNF-), which damage the lungs' microvasculature and cause endothelial dysfunction, hemostasis disturbances, and pulmonary thrombi. The second alternate theory is that systemic thrombosis is caused by the virus's direct or indirect impact on coagulation pathways.^{13,14}

A recent meta-analysis found a link between COVID-19 severity and many inflammatory biomarkers (such as C-reactive protein (CRP), procalcitonin, interleukin (IL-6) and ferritin).¹¹

In the present study patients with Covid 19 have high levels of D-dimer and most studies have demonstrated that COVID-19 patients had considerably higher levels of D-Dimer, C-reactive protein (CRP), and fibrinogen. D-dimer can predict the likelihood of deep vein thrombosis and patient death and be strongly correlated with the severity of the condition. As the severity of the disease progressed, the coagulation indicators increased significantly in COVID-19 patients. Thus by monitoring changes in laboratory markers and timely adjusting the anticoagulant dose, the clinical administration of COVID-19 patients provides a justifiable basis for administering anticoagulation therapy.¹⁵⁻¹⁸

To our knowledge, no study, to date, has addressed the effect of curcumin on the D-dimer and thrombotic sequelae in patients with Covid-19. Thus, because of the potential effect of curcumin on inflammation and its capacity to act as an anti-viral as well as its previously reported effect on cardiovascular and lung health, as one early study reported that treatment with Curcumin resulted in early symptomatic recovery (fever, cough, sore throat, and breathlessness), less deterioration, fewer red flag signs, better clinical results for patients and the capability to sustain oxygen saturation above 94% on room air in patients with mild, moderate, and severe symptoms.^{8,19,20} we chose to explore its effect on cases of Covid-19 with a mild to moderate rise in D-Dimer serum level

Our results showed that using curcumin as an adjunct to enoxaparin exhibits a better overall outcome than using enoxaparin by itself with the added benefit of high safety profile these findings reinforce the finding of other studies that investigated the antithrombotic properties of curcumin and how it reduces thrombosis in mice by adjusting platelet counts, D-dimer, and plasminogen activator inhibitor-1, as well as the anticoagulant qualities of curcumin and its derivative (bisdemethoxy curcumin, BDMC), which were assessed by tracking the activities of cell-based thrombin and activated factor X (FXa) generation, prothrombin time (PT), and activated partial thromboplastin time (aPTT). The results demonstrated that curcumin and BDMC significantly prolonged aPTT and PT and inhibited thrombin and FXa activities.²¹⁻²³

CONCLUSION

The overall results of this clinical study showed a significant D-dimer reduction by curcumin supplementation. These findings uphold the idea that this polyphenol has the potential in attenuating coagulopathy and mitigate disease severity. Moreover, clinical trials with curcumin demonstrated safety, durability, and nontoxicity. Thus, it sounds rational to consider the treatment of COVID-19 and its complications with highly effective nutraceuticals such as curcumin even alone or as an adjunct to other best-known treatments of it.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Maiss S. Baqer, Saifan A Dushan, Rafif Raad
Drafting or Revising Critically:	Rabab Mohammed Noori Hameed, Ayaashraf Ahmed, Basim Dhawi Dakhil
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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