Tranexamic acid in COVID-19 pneumonia

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Abstract

Since the beginning of the current coronavirus 2019 (COVID-19) outbreak, an intense number of studies have been done in an attempt to discover effective therapies, not only from the point of view of discovering new drugs, but also from its repurposing. Recent studies have proposed tranexamic acid (TXA), a hemostatic drug widely used in clinical practice, as a potential therapeutic option for COVID-19 as it reduces plasmin levels. Thus, this letter to the editor aims to provide a critical overview on the use of TXA in the treatment of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection.

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Abstract

Since the beginning of the current coronavirus 2019 (COVID-19) outbreak, an intense number of studies have been done in an attempt to discover effective therapies, not only from the point of view of discovering new drugs, but also from its repurposing. Recent studies have proposed tranexamic acid (TXA), a hemostatic drug widely used in clinical practice, as a potential therapeutic option for COVID-19 as it reduces plasmin levels. Thus, this letter to the editor aims to provide a critical overview on the use of TXA in the treatment of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection.

Dear Editor,

Since the beginning of the current coronavirus disease 2019 (COVID-19) outbreak, an intense number of studies have been done in an attempt to discover effective therapies, not only looking from a point of view of new drugs discovery but also drug repurposing. Recently, Chan et al. [1] reported that tranexamic acid (TXA) is a potential therapeutic option for COVID-19 as it reduces the plasmin levels, important in cleaving

the surface protein (SP) of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Their idea that the plasmin inhibition might attenuate the disease progression is striking and attractive since anti-plasmin drugs may reduce the SARS-CoV-2-associated complications [2]. In the same manner, Baeker et al. [3] also reported that high plasmin activity increases the SARS-CoV-2 virulence while facilitate its entry and replication, thus anti-plasmin drugs may prevent COVID-19 progression.

Briefly, TXA is a hemostatic drug in clinical practice and available as both oral and intravenous forms and prescribed even for outpatients. It is of concern and alarm that some non-professional and non-medical readers of article published by Chan et al. [1] might be apt to and tend to take TXA alone against COVID-19 in anticipation of its anti-plasmin effect. But, as all drugs, TXA also has adverse effects, with venous and arterial thrombosis being stated as major effects by different studies [4, 5]. Chan et al. [1] also illustrated that TXA has anti-inflammatory effects via inhibition of plasmin-mediated activation of neutrophils, monocytes, complement system and tumor necrosis factor alpha (TNF-α). Besides, TXA modulates coagulopathy via suppression of fibrinolysis, and thus may prevent COVID-19 induced disseminated intravascular coagulopathy (DIC) [6]. Therefore, anti-coagulants should be co-administrated with TXA when used as an anti-inflammatory agent to prevent DIC, as it may be fatal since administration of TXA alone may exacerbates both organ and tissue damage in DIC mice models [7]. Moreover, and worth of note is that, venous thromboembolism and DIC have been linked to COVID-19 in about 20-30% and 70% of cases, respectively [8]. Furthermore, it has been shown that SARS-CoV-2 trigger inflammatory and endothelial cells for inflammatory cytokines and pro-coagulants production and release, such as Von Willebr and tissue factors, leading to fibrin clots' formation. These changes activate platelets and fibrinolysis with subsequent DIC onset [9].

Tang et al. [9] also showed that DIC is linked to a poor prognosis and high mortality in COVID-19 patients, since plasma fibrinogen levels and anti-thrombin activity are reduced while D-dimer level is increased. By itself, low fibrinogen and high D-dimer plasma levels are associated with a high risk of acute respiratory distress syndrome (ARDS) [9]. Venous thromboembolism (VTE) and pulmonary embolism have also been reported in COVID-19 patients (in around 25%) [10]. Besides, arterial thrombosis has been reported and manifested as myocardial infarction, ischemic stroke and limb ischemia [11].

The pathophysiology of thrombus formation in COVID-19 is mainly linked to cytokine storm and endothelial dysfunction that together led to DIC, hypercoagulation and ARDS [12]. Bester et al. [13] confirmed that high levels of interleukin (IL)-6 and other pro-inflammatory cytokines are associated with noteworthy disorders in coagulation/fibrinolysis axis. So, COVID-19-induced cytokine storm and associated DIC is more prevalent and directly correlated with ARDS. Thus, the administration of TXA for its weak anti-inflammatory and anti-plasmin effects in COVID-19 management may worsen preexistence DIC and should be weighed against its benefit.

Previously, Tucker et al [14], even before the COVID-19, underlined that fibrinolytic system is inhibited during acute lung injury (ALI) and ARDS due to an increase in plasminogen activator inhibitor-1 (PAI-1) levels in the bronchoalveolar fluid and plasma. Thus, pulmonary fibrinolysis' restoration by intravenous plasmin or urokinase administration trigger a reduction in both ALI and ARDS severity [15]. Herein, TXA administration may aggravate ALI and ARDS in COVID-19 patients as it suppresses the plasmin effect, which has a great role in removing necrotic proteins and improving lung oxygenation [15]. Taken together, data presented here underline that TXA therapy in COVID-19 patients depend on its antiviral merit, with its administration might be balanced against the risk of DIC and PE, despite a meta-analysis of previous trials indicated that TXA therapy has no thrombotic risk [16].

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Conflict of interest

There are no conflicts of interest

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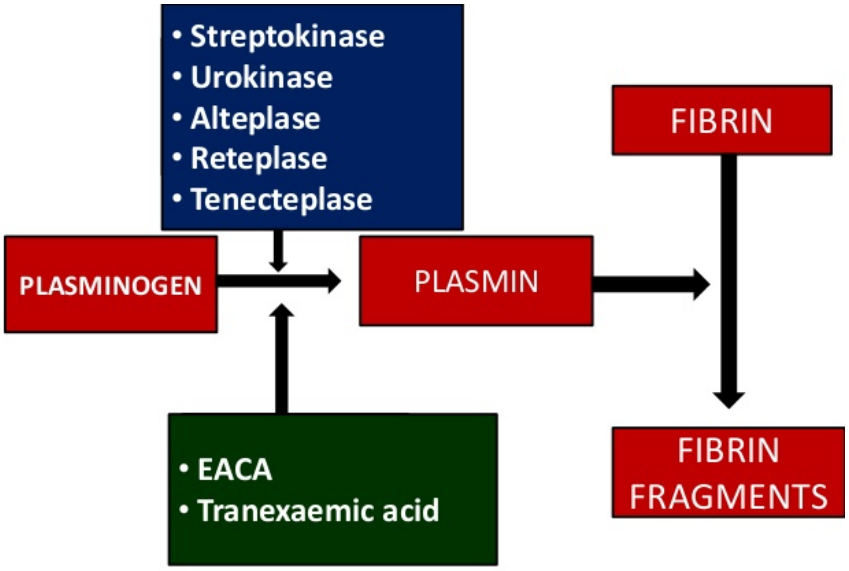

Figure 1. Mechanism of action of tranexamic acid.