Review Article

Use of Tranexamic Acid in SARS-COV-2: Boon or Bane?

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ABSTRACT

The devastating pandemic of SARS-CoV-2 (COVID-19) began in Wuhan, China, and spread rapidly through most parts of the world in the second half of 2020. The air droplet spread of SARS-CoV-2 is of great global health concern as it is potentially fatal. Various drugs and treatment modalities have been tried to date, but none have been found to be definitive. Tranexamic acid (TXA) is commonly used in pigmentary disorders in dermatology due to its ability to reduce melanocyte tyrosinase activity. It also possesses anti-fibrinolytic and anti-inflammatory properties, which have been observed to suppress the cytokine storm and modulate coagulopathy in patients suffering from COVID-19. TXA, when administered early, has been effective in decreasing the severity of symptoms in COVID-19 patients, but on the contrary, it has also been associated with life-threatening thrombosis when given as a single drug.

Keywords: COVID-19, SARS-CoV-2, Tranexamic acid

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1. Introduction

The International Committee on Taxonomy of Viruses named a new virus that has shivered the world with its global health hazards and varied manifestations as SARS-CoV-2 on February 11, 2020. On March 11, 2020, the World Health Organization issued alerts to all countries regarding SARS-CoV-2, declaring it a global health emergency with worldwide mortality counting over 19 million and likely crossing 30 million by the end of the year (1). High mortality and morbidity can be caused by increased fibrin degradation products and thrombocytopenia due to hyperfibrinolysis, which can lead to hemorrhage in multiple organs. Tranexamic acid (TXA), a well-known antifibrinolytic drug, was first described in 1962 by Japanese researchers Shosuke and Utako Okamoto (2). Being a synthetic derivative of the amino acid lysine, it acts by blocking the lysine binding sites on plasminogen molecules (3). The indications of TXAs are myriad. It is frequently used to control bleeding in menorrhagia, epistaxis, postoperative blood loss in procedures such as total knee replacement, adenoidectomy, tonsillectomy, and dental procedures, as well as upper gastrointestinal bleeds and hemophilia (4). TXA has a great role in the treatment of melasma, hereditary angioneurotic edema, and ultraviolet (UV) light-induced hyperpigmentation, in addition to its primary use as an antifibrinolytic (4,5). Recently, it has transpired as a drug against SARS-CoV-2. Research has found that plasmin and other proteases cleave the spike proteins (S proteins) of SAS-CoV-2, leading to increased infectivity and virulence; therefore, a drug inhibiting plasmin (ogen) may inhibit the entry of viruses, instigating low infectivity and virulence (6).

2. Results

2.1. Antifibrinolytic Mechanism of Action

TXA is a synthetic analogue of lysine that prevents the binding of plasminogen to fibrin, thereby inhibiting the conversion of plasminogen to plasmin and reducing the risk of hemorrhage. At higher doses, TXA can directly inhibit plasmin (7). Another of TXA's mechanisms of action is blocking the binding of α2 antiplasmin and thus inhibiting inflammatory reactions. TXA can be administered orally, intravenously, topically, and intralesionally. Elimination is mainly via renal clearance (approximately 95%) and has a half-life of 2.3-3 h (7, 8) (Figure 1).

2.2. Tranexamic Acid in Dermatology

The use of TXA in dermatology was first reported in 1979, when Nijo Sadako tried it as a treatment modality in patients with chronic urticarial disease (9). Various formulations used in dermatology are oral, intradermal, and topical, with or without microneedling.

2.3. Dermatological Mechanism of Action

UV exposure increases the production of plasminogen activators in the epidermal keratinocytes (10). TXA inhibits the formation of plasmin by blocking plasminogen. Plasmin is responsible for the release of arachidonic acid and α melanocyte-stimulating hormone intracellularly, which has the potential to stimulate melanogenesis (11). As TXA acts by inhibiting plasmin, it inhibits melanogenesis by depleting the arachidonic acid within the keratinocytes (12, 13). UV exposure can directly stimulate keratinocytes to release prostaglandin E2 (PGE2), which stimulates tyrosinase action and the development of dendrite growth within melanocytes. TXA tends to inhibit the production of PGE2 and tyrosinase (14, 15). TXA is also known to decrease the production of vascular endothelial growth factor and basic fibroblast growth factor, which are known as angiogenic factors. These factors lead to the release of arachidonic acid and plasminogen from epidermal keratinocytes and thus lead to melanogenesis (16, 17). There is an autosomal dominant genetic disorder known as hereditary angioedema (HAE), which mostly results from the deficiency of an enzyme inhibitor of C1 esterase. Two clinical types have been described for this disorder. Type I HAE is the most common type and occurs due to the deficiency of C1-INH, whereas Type II HAE is caused by the dysfunction of C1-INH. Symptoms last for 2-5 days and include localized subcutaneous/submucosal edema, especially in the extremities, face, genitals, trunk, and abdomen, which are caused by the genetic mutations of factor XII, plasminogen, and angiopoietin-1. It may cause a life-threatening condition known as laryngeal edema (18). Normally, plasmin is inhibited by C1-INH, but in HAE, there is an uninhibited formation of plasmin. TXA binds to plasminogen and inhibits the formation of plasmin. TXA also helps in attenuating the symptoms of HAE by blocking the activation of the complement system and immune cells (Figure 2).

2.4. Tranexamic Acid against SARS-CoV-2

Ji et al. reported that the virulence and infectivity of SARS-CoV-2 increase when the S protein of the virus is cleaved by plasmin. Therefore, if a drug can inhibit or suppress plasmin (ogen), it can also prevent disease progression (6).

2.5. Anti-SARS-COV-2 Mechanism of Action-

The SARS-CoV-2 strain has a receptor domain structure in the S protein. Plasmin and tissue protease cleave the S protein into S1 and S2 subunits. The S1 region on the S protein leads to the binding of protein to the host cell ACE2 receptors, whereas the S2 region is responsible for the fusion of cell membranes with viral RNA, leading to high virulence (19). TXA acts by inhibiting plasmin and modulating coagulopathy, and by blocking plasmin,

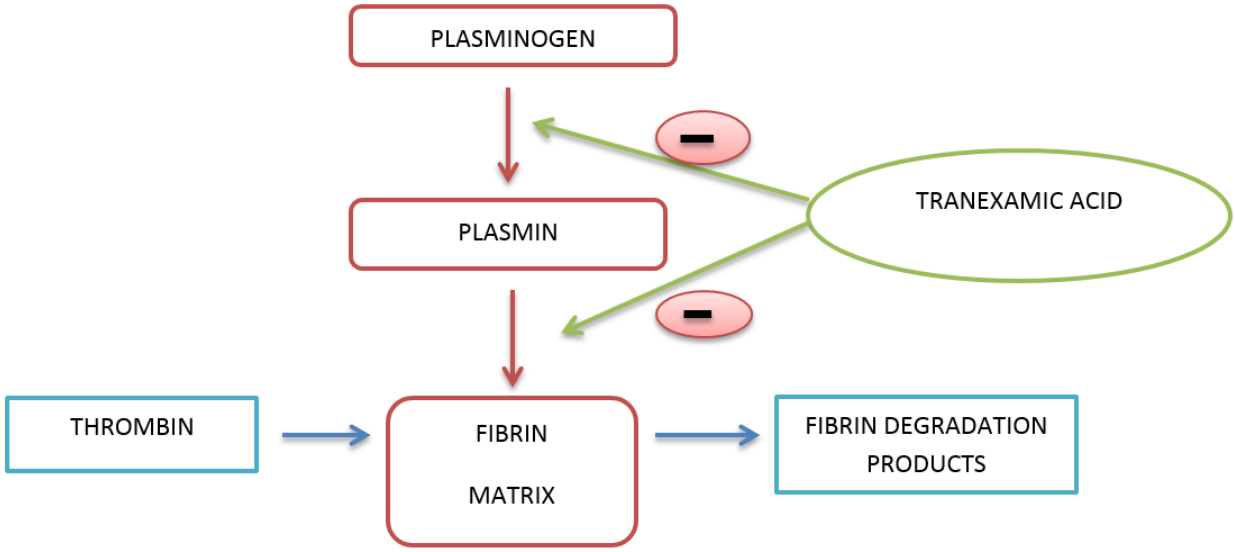

Figure 1: Antifibrinolytic mechanism of action of Tranexamic Acid

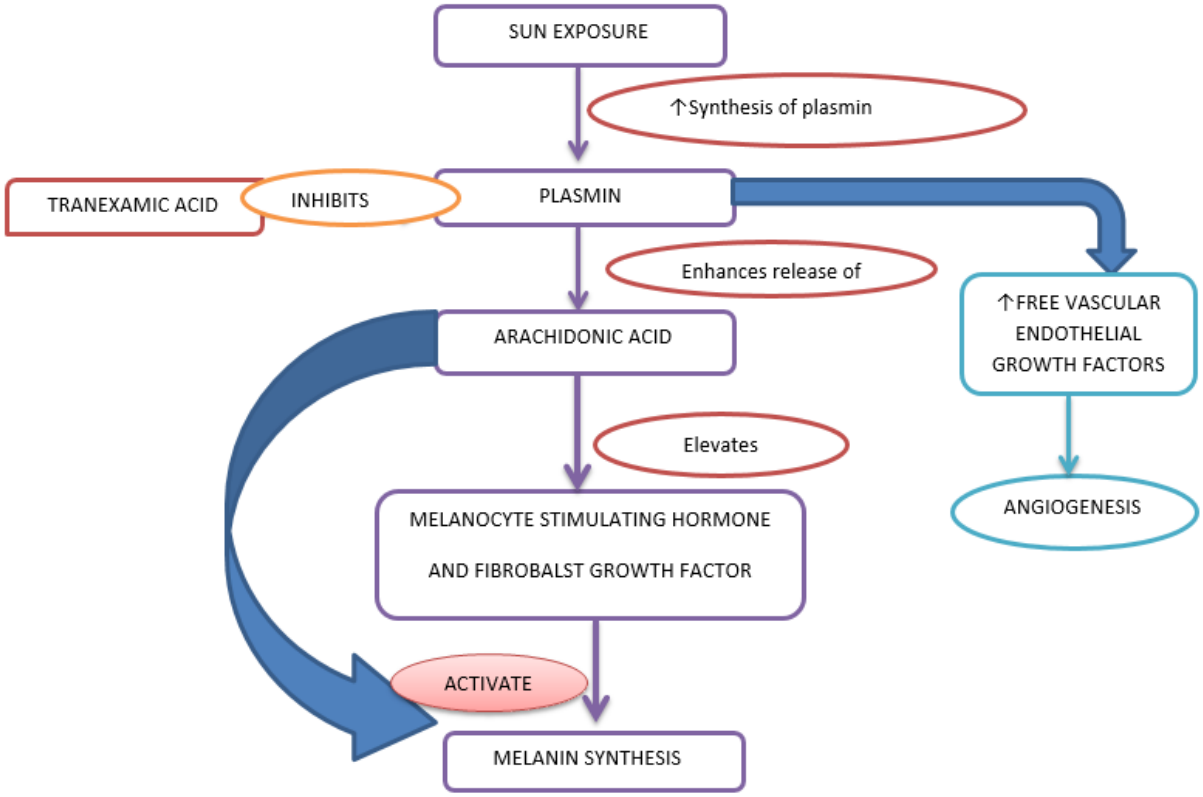

Figure 2. Mechanism of tranexamic acid in dermatology

Blocking plasmin also leads to inhibition of plasmin mediated activation of complements, monocytes and neutrophils, modulation of cytokines and cellular immunity hence anti-inflammatory mechanism of action. (20) (Figure 3). Chan KH et al. reported a case in May 2020 of an 82-year-old patient who had COVID-19 but did not develop severe symptoms or cytokine storms even though he had multiple health conditions, such as hypertension, coronary artery disease, prostate cancer, and myelodysplastic syndrome. This was assumed to be due to the intake of TXA by the patient since October 2019 (21). Being a commonly used, inexpensive drug that can be a boon in the current pandemic, TXA also has various adverse effects and contraindications (Table 1). A few of the adverse effects include gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, hypotension/dizziness following fast intravenous administration, allergic skin reactions, temporal vision impairment, convulsions, and thromboembolism. SARS-CoV-2 induces coagulation disorders, which can lead to both bleeding and thrombosis. It has been noticed that critically ill patients have remarkably high levels of D-dimer, international normalized ratio (INR), and thrombocytopenia. Barker and Wagener reported that TXA is unlikely to cause thrombotic complications when administered for melasma; however, several reports have shown that the single administration of TXA without simultaneous use of anticoagulants can lead to disseminated intravascular coagulation, resulting in systemic thrombosis, which can be life-threatening (22, 23, 24, 25).

3. Conclusion

TXA has been used since ages ago for the prevention and treatment of bleeding due to various causes and also as a paramount treatment modality in melasma, hyperpigmentation, and hereditary angioedema. The TXA mechanism of action in SARS-CoV-2 looks promising. The early administration of TXA can prevent or decrease the severity of symptoms, but due to the hypercoagulability caused by COVID-19, solitary use of TXA can lead to life-threatening thrombosis. To use the beneficial mechanism of action of TXA and to maximize the effects and minimize the adverse effects of it, a few important factors, such as patient selection (mild symptoms, normal coagulation profile, and D-dimer) and concomitant use of anticoagulants, should be considered to prevent its dreaded complications.

Table 1. Contraindications of tranexamic acid.

Absolute	Relative
Hypersensitivity to tranexaemic acid	Breast-feeding
Pregnancy	Patients with acute promyelocytic leukaemia using all-trans retinoic acid
Active thromboembolic disease: Pulmonary embolism, cerebral thrombosis, Deep Vein thrombosis	Renal/hepatic impairment: may require dose adjustment
Personal or family history of thromboembolism	Concomitant use with the oral contraceptive pill.
Renal failure	
History of convulsions	
Acquired disturbances of colour vision	
Fibrinolytic conditions due to consumption coagulopaths	

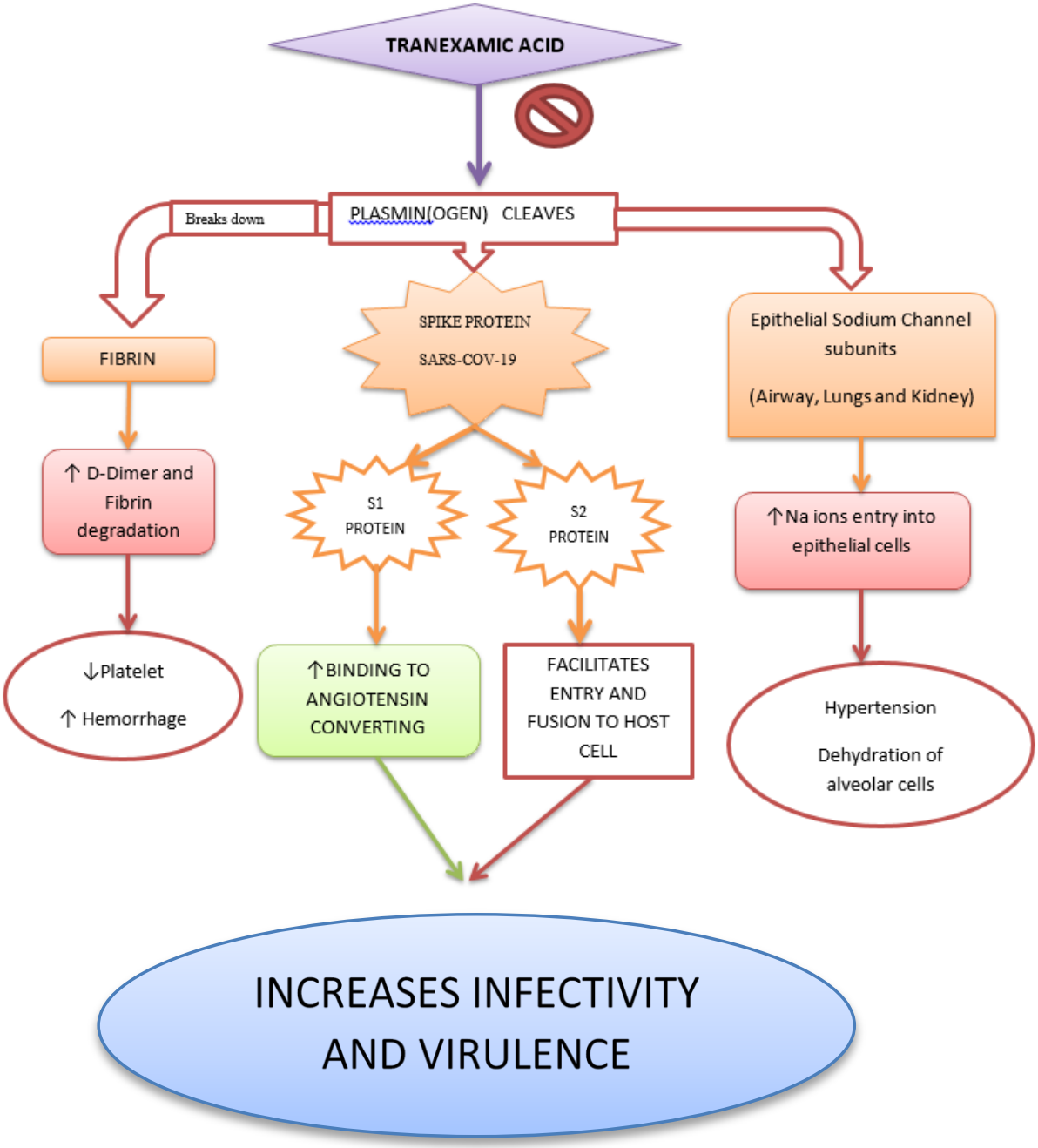

Figure 3. Anti SARS-CoV2 Mechanism of Action of Tranexamic Acid**.**

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Not Applicable.

Authors' Contribution
Study concept and design: M.C., A.K.S., S.M.
Acquisition of data: M.C., R.K.M., P.S., A.S.
Analysis and interpretation of data: M.C., B.D.K, S.J.
Drafting of the manuscript: M.C., R.K.M., P.S., A.S.
Critical revision of the manuscript for important intellectual content: M.C., A.K.S., S.M., B.D.K.
Administrative, technical, and material support: M.C., R.K.M, S.J.

Ethics
We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest
The authors declare that they have no conflicts of interest.

Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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