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Mini-Review Article

Journal of Current Trends in Nursing & Health Care

Zinc-Induced Neurological Anti-Thrombosis and Thrombolysis in Children Under Severe Covid-19 Infective Pandemic

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Received Date: 24 June, 2021
Accepted Date: 07 July, 2021
Published Date: 13 July, 2021

Citation: Tsuneo Ishida (2021) Zinc-Induced Neurological Anti-Thrombosis and Thrombolysis in Children Under Severe Covid-19 Infective Pandemic. J Cur Tre Nur Health Care 2(2): 1-9

Abstract

Zinc (II) induced pediatric neurological anti-thrombosis during ROS production and thrombolysis activities during free radicals generation are discussed under the COVID-19 pandemics, and these Zn^{2+} ions-binding molecular proteins mechanism on neural anti-thrombus formation and thrombolysis activity has been clarified.

Zinc intakes by zinc induced immunity are required 3 mg/day for 7 months to 3 years, 5 mg/day for 4 ~ 8 years, and 8 mg/day for 9 ~13 years in children. Supplementation have also been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the RDI for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years. The other, the normalization of Zn^{2+} intake in stroke patients with low mineral intake may enhance neurological recovery with recommended zinc neurological intake of 10 mg/day. Zinc reduces neurological resultings in pediatric COVID-19 patients that Zn^{2+} ions promote inflammatory cytokine as a neuro-degenerative disorder and that zinc ions could modulate coagulopathy by hypercoagulation and the microangiopathy, Zn^{2+} induced platelet-dependent fibrin formation lead to modulation of neurological thrombus formation, Zn^{2+}-induced platelet activation enhances anti-thrombus growth. Zinc (10-20 mg daily) could modulate hypercoagulation and subsequent COVID-19 neurological thrombus formation. The other, thrombolysis activity by zinc and its chelator, and some other thrombolytic drugs are showed that the thrombolytic effect significantly increases the effect of streptokinase-induced thrombolysis and the thrombolytic drugs have been used as zinc induced COVID-19 thrombolytic therapy.

Zinc induced reactive oxygen species (ROS) production and oxidative stress in COVID-19 thrombosis in children that are caused by mRNA degradation and oxidative respiratory burst, and thrombosis revoluted by tissue damage and ROS resolve venous thrombus. The other, zinc induced free radicals generation and oxidative stress in COVID-19 thrombolysis that free radicals are produced in pediatric body by various endogenous systems, exposure to different physiochemical conditions or pathological states displayed dominant thrombolytic action.

Accordingly, Zinc (II) ions-binding proteins molecular mechanism on anti-thrombosis and thrombolysis is clarified that Zn^{2+} ions may be bound with COVID-19 molecular proteins such as COVID-19 surface protein, platelet-dependent fibrin protein, blood cllotting protein, thrombus protein, and thrombolytic proteins by Zn^{2+} ions-centered tetrahedrally coordinated binding protein pattern.

Keywords: Zinc-Induced Pediatric Immune and Neurological Intake, Anti-Thrombus Formation and Growth, Thrombolysis, Thrombolytic Drugs, ROS and Free Radicals Generation, Zn^{2+} Ions-Coordinated Pattern

Introduction

COVID-19 anticoagulation is often associated with hypercoagulability and disseminated intravascular coagulation (DIC) that this hypercoagulability is manifested as progressive lung and kidney disease, pulmonary emboli (PE), venous thrombotic events (VTE) in adults. Characteristic of pediatric thrombosis is with thrombus localization of lower limb deep venous thrombosis or pulmonary embolism [1]. The other, thrombolytic therapy in children can be considered for patients with a hemodynamically unstable pulmonary embolus or limb-threatening deep vein thrombosis and decision making for thrombolytic therapy be a coordinated approach involving the critical care team, hematologists [2]. Both thrombosis and thrombolysis processes in children are important that the thrombosis has the characteristic blood clotting disorders and the thrombolysis should be used the recombinant tissue plasminogen activator (t-PA) efficacy of thrombolysis in children [3,4]. The pediatric thrombosis is anticoagulation that reported on the use of systemic thrombolysis, endovascular

thrombolysis, and mechanical thrombectomy. Thrombolysis is indicated in the setting of life- or limb-threatening thrombosis. Thrombolysis can rapidly improve venous patency thereby quickly ameliorating acute signs and symptoms of thrombosis and may improve long-term outcomes such as post-thrombotic syndrome [5].

Epidemiological and clinical characteristics for a rapid aggravated disease against severe SARS-CoV-2 or acute COVID-19 infection are associated with many difficulties due to thrombus formation and growth by blood coagulation and thrombolysis activities. The recently global COVID-19 and the coronavirus varient RNA (SARS-CoV-2 RNA mutation) pandemics have been needed as an urgent search for effective medical scientific improvements, in which the risk of severe infectious SARS-CoV-2 and the RNA mutation increases with pulmonary blood thromboembolism in COVID-19 disease, and the infectious infant diseases increase, including being associated with lower zinc status. Thus, these difficulties must be overcome by the development of the medical and scientific theory and the many efforts. SARS-CoV-2 virus and the clinical disease COVID-19 in children are characteristic that minor contributors to virus transmission and differential expression of ACE2 in children which may attenuate viral entry, and host-virus factors that underpin the unique aspects of SARS-CoV-2 pathogenicity in children [6]. Children with SARS-CoV-2 infection have less severe coronaviruses disease-19 (COVID-19) than adults [7]. However, when children become have acute COVID-19 under the pandemonium, children with comorbidities have a higher risk of severe COVID-19 than children without underlying disease, in which childhood obesity is likely positively correlated with COVID-19 severity that pediatric underlying conditions play in COVID-19 severity [8]. Pediatric patients with COVID-19 infection are shown that the infected children had coinfection with other common respiratory pathogens and the pediatric patients have prolonged fecal shedding of SARS-CoV-2 RNA during the convalescent phase that most pediatric patients had relatively mild disease with good prognosis, which could be seen in children infected with SARS-CoV respiratory viruses with innate immunity in response to the pathogen [9]. COVID-19 in children is relatively mild that it is easy to miss the diagnosis in the early stages when present with a non-respiratory disease. The other, severe COVID-19 can also occur in children with underlying or coexisting diseases that the possibility of SARS-CoV-2 infection should be suspected when children show digestive tract symptoms, especially with a severe systemic inflammatory reaction [10]. Pediatric cases of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 are relatively fewer cases of COVID-19 among children compared to cases among adult patients. The mild disease in children may be related to trained immunity that refers to the use of certain vaccines [11].

In the case of severe pediatric COVID-19 pandemic infection, severe thrombocytopenia and acute respiratory distress syndrome (ARDS) are presented, including patient's severe disease course was associated with thrombocytopenia and elevated inflammatory markers. Finally, randomized placebo controlled clinical trials were used to study drugs like tocilizumab and remdesivir to include children in addition to adults with COVID-19, in which this COVID-19 thrombus inhibition in inflammatory and respiratory ailment has been becoming recently important matters in SARS-CoV-2 infectious pandemonium [12]. In addition, the neurological abnormalities reported in children caused by this viral infection and the characteristics of the neurologic manifestations had been shown in neurologic complications and disorders under the COVID-19 severe respiratory illness. Hence, more comprehensive epidemiological studies are required in large populations to accurately quantify the incidence of these complications and treatment of COVID-19–related neurologic syndromes [13].

On the other hand, zinc utilization to pediatric antivirus activity becomes effective for children's health that zinc-binding proteins such as the metallothioneins may possess antiviral roles [14]. Zinc is an antioxidant that protects cells from the damaging effects of oxygen radicals generated during immune activation. The adverse effects of zinc deficiency on the immune system are likely to increase the susceptibility of children and lead to a zinc-deficient state. Therefore, zinc supplementation could conceivably modulate the immune and inflammatory responses to viruses in a way that are beneficial to the host [15]. The demonstrated preventive therapeutic effect of zinc in the treatment of childhood pneumonia is conflicting that Zn supplementation in 2~24 months old children with radiologically verified pneumonia did not result in significant improvement of risk reduction of treatment failure. Moreover, Zn supplementation in Zn-deficient children with pneumonia until the achievement of normal serum Zn levels did not improve the clinical appearance of the disease [16].

In this mini-review, zinc-immune and neurological pediatric anti-viral activity for SARS-CoV-2 prevention, COVID-19 defenses of severe respiratory and acute pneunomary disease, and zinc induced neurologic COVID-19 anti-thrombus formation, and thrombolysis with nervous COVID-19 in children are discussed during ROS production, free radicals generation, and oxidative stress. Subsquently, the Zn-binding molecular proteins mechanism on anti-thrombosis and thrombolysis is clarified.

Zinc-Induced Immunity and Neural Reduction of Covid-19 Infection in Children

Zinc intakes by zinc induced immunity are known to be required 3 mg/day for 7 months to 3 years, 5 mg/day for 4 ~ 8 years, and 8 mg/day for 9 ~13 years in children. Zinc induced immunity in humans, high zinc concentrations are found in the retina (3.8 μg/g dry weight), choroid of the eye (274 μg/g) and in bone (100–250 μg/g), while only 1 μg/mL zinc is found in plasma, which equals around 0.1% of total body zinc. Zinc binding to those proteins can activate or inactivate their activity, or change characteristics important for substrate binding. Thus, zinc homeostasis is crucial for an adequate function of the immune system and result in severe disturbances in immune cell numbers and activities that the role of zinc in regulating intracellular adaptive immune cells. Main underlying molecular mechanisms affected by altered zinc homeostasis, the interplay of zinc homeostasis and the redox metabolism in affecting intracellular signaling will be emphasized [17].

Neurobiological roles of endogenous zinc in neurodegenerative diseases have the considarable evidences that free Zn^{2+} in the extra-cellular fluid induces amyloid deposition, a neuroprotective against the zinc-mediated injury in stroke, and possible neuroprotectant with specificity against zinc-mediated injury is tissue plasminogen activator tPA, which is currently used for thrombolysis in human patients [18]. The normali-zation of Zn^{2+} intake in stroke patients with low mineral intake may enhance neurological recovery with zinc neurological intake of 10 mg/day [19]. Neurological complications of SARS-CoV-2 infection in children are much less frequent that children with SARS-CoV-2 multisystem inflammatory syndrome are especially at risk for neurological complications and COVID-19 pandemic

impact on the healthcare system of some countries, neurological conditions, attention deficit and hyperactivity disorder (ADHD), and neurologic thrombosis [20]. A pediatric patient with coronavirus disease COVID-19 associated with multiple cerebral venous sinus thrombosis and venous infarction has some cases of deep vein thrombosis and pulmonary thromboembolism in COVID-19. However, this is a rare case of cerebral venous sinus thrombosis in a patient diagnosed with the novel coronavirus. the thrombus in SARS-CoV-2 infection has been related with a hypercoagulable state and potential thrombogenic risk. It is believed to be due to the inflammatory response induced by the viral infection with endothelium dysfunction and tissue factor expression, which promotes a coagulation activation and possible thrombi formation and hyperfibrinolysis [21]. Zinc may reduce neurological consequences in COVID-19 patients that Zn^{2+} may promote inflammatory cytokine storms and the coronaviruses can affect the nervous system through blood circulation and cause neuroinflammation. Hence, COVID-19 in neurological disorders can present with a large increase in systemic pro-inflammatory cytokines as a neurodegenerative disorder that cause neuroinflammation [22].

Zinc-Immune Pediatric Prevention for Respiratory Function and Pneumonia Against Covid-19 Infection

As the minor receptors for children may cause low risk against severe COVID-19 infection, the ACE2 for children is involved that ACE2 is particularly within the lung microenvironment, where ACE2 levels are intrinsically elevated that SARS-CoV-2 host cell entry plays an integral role in the endothelial inflammatory response. Low SARS-CoV-2 morbidity and mortality, ACE 2 distribution that potentially limits viral entry and subsequent inflammation and tissue injury, the role of children in virus transmission, and host-virus factors that underpin the unique aspects of SARS-CoV-2 pathogenicity in children [23].

Zinc deficiency was very mild (3 to 5.0 mg Zn intake during the zinc-restricted period), the plasma zinc concentration remained more or less within the normal range and it decreased only after 4~5 months of zinc restriction. The other, zinc concentrations in lymphocytes, granulocytes, and platelets decreased within 8~12 weeks, suggesting that the assay of cellular zinc provided a more sensitive criterion for diagnosing mild deficiency of zinc, in which zinc enhances the upregulation of mRNA, which in both young adults and elderly subjects, zinc supplementation decreased oxidative stress markers and generation of inflammatory cytokines [24]. A range of zinc supplementation has been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the recommended daily intake (RDI) for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years [25]. Zn supplementation significantly decreased the incidence of acute lower respiratory infection (ALRI) defined according to specific clinical criteria in children aged <5 years that zinc reduced childhood with ALRI, but the effect was null if lower specificity case definitions were applied, however, the factor was remained unexplained. Zinc induced pediatric preventing respiratory 2019-nCoV is required as supplementation with 10 mg zinc gluconate that effectiveness of zinc gluconate supplemen-tation for 2 months period compared to placebo in reducing respiratory morbidity in acute lower respiratory infected children up to 5 years of age living in zinc poor population [26]. Zinc supplement may result in significant reduction in respiratory morbidity among children with acute lower respiratory infections [27]. Pediatric zinc supplementation for more than 3 months could be effective in preventing pneumonia in children younger than 5 years of age, although the evidence was not robust enough to advocate prophylactic properties if given for shorter periods of time [28]. The effectiveness of zinc supplementation should be assessed for acute pneumonia provided that cases are well-defined by strict clinical criteria. Thus, zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia [29]. Preventing pneumonia is required that zinc supplementation alone (10 to 20 mg), for more than 3 months, was associated with a significant reduction in the rate of pneumonia by 19%, with Risk Ratio (RR) of 0.81 (95% CI 0.73 to 0.90). Mortality was not statistically different (RR = 0.85; 95% CI 0.65 to 1.11) [30].

Antiviral Activity of Zn^{2+} Ions in Children with Severe Respiratory Covid-19 Infection

Zn supplementation of 30 mg/day in Thai children reduced significantly severity of acute lower respiratory tract infections resulting in faster disease cessation and shorter hospital stay [31]. A decrease of 15% (0.78-0.94) in days and 12% (0.78-0.94) in duration of episode in acute respiratory infections was observed. Incidence of acute lower respiratory infections decreased by 62% (0.26-0.36) and the effect remained for full five months of follow up. Prophylactic zinc supplementation for two weeks may reduce the morbidity due to acute lower respiratory infections but not overall rate of acute respiratory infections in infants aged 6□11 months in similar populations [32].

Serum zinc level was very low (25.19 ± 15.49 μgmol/L) with acute respiratory infection (ARI) children as compared that (55. 51 ± 31.15 μgmol/L) with non-ARI children, in which environment and nutritional status were found to be prevalently associated with higher incidence of acute respiratory infections and serum zinc content had been varied with corresponding sociodemographic, nutritional and health care profile [33].

Antiviral Avtivity of Zn^{2+} Ions in Children with Covid-19 Acute Pneumonia

Pneumonia is one of the most common implications of lower respiratory tract involvement that adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children, and could help reduce antimicrobial resistance by decreasing multiple antibiotic exposures, and lessen complications and deaths where second line drugs are unavailable. 20 mg zinc per day can accelerate the recovery from severe pneumonia in children [34]. The effect of zinc on clinical course of 3 to 60-month children hospitalized due to pneumonia was assumed that this element was effective in resolving clinical symptoms and duration of hospitalization. Zinc supplements given during an acute episode are not beneficial in short-term clinical recovery from severe pneumonia in hospitalized children. Primary outcome was recovery from pneumonia which included the incidence and resolving clinical symptoms and duration of hospitalization [35]. Zinc may have improved their nutritional status, specially 30 mg/day of zinc supplementation reduces pneumonia in children with chronic kidney disease (CKD) [36]. Zinc supplementation + Chloroquine (CQ)/hydroxychloroquine (HCQ) may be more effective in reducing COVID-19 morbidity and mortality than CQ or HCQ in monotherapy [37].

The serum zinc level returned to a normal level (median, 53.20 μmol/L) on day 12 ± 2 in the treatment. There was no statistical difference in the pediatric critic illness score, lung injury score, length of hospital stay, and duration of mechanical ventilation between the zinc treatment [38]. The mean serum zinc in patients

was normal (80.77 + 25.3 μg/dL) yet, the mean serum zinc level in pediatric intensive care unit (PICU) patients was lower than that of general ward patients that the lower the serum zinc level, the higher the grade of respiratory distress among children with pneumonia [39]. Zinc sulfate plus hydroxychloroquine may play a role in therapeutic management for COVID-19 without PICU [40].

Zinc Prevents Thrombus Formation

Zinc can prevent COVID-19 thrombosis that the contribution of extracellular or intracellular Zn^{2+} to megakaryocyte and platelet function and dysregulated Zn^{2+} homeostasis in platelet-related diseases by focusing on thrombosis, ischemic stroke and storage pool diseases. Consequently, zinc ions can impair the coagulation pathway and fibrin clot formation in humans, which can be more critical in patients with combined defects of both α and δ-granules or with thrombocytopenia [41]. For anticoagulation therapy in COVID-19 patients with children and adolescents below 18 years, the anticoagulation chemoprophylaxis with enoxaparin for patients with moderate, severe, and critical COVID-19 are indicated critically ill, intensified anticoagulation with therapeutic dose [42].

COVID-19 is associated with hypercoagulability and disseminated intravascular coagulation (DIC). Children infected with SARS-CoV-2, with noted elevations in D-dimer and maximum clot firmness (MCF) on rotational thromboelastometry (ROTEM), indicating hypercoagulability that ROTEM testing is feasible and recommend that its utility in determining the hypercoagulable state merits further study in children, who have shown can exhibit clinical severity and laboratory evidence of a coagulopathy identical to that seen in adults with SARS-CoV-2 [43]. This thrombotic microangiopathy (TMA) in children with SARS-CoV-2 has been observed that a high proportion of tested children with SARS-CoV-2 infection had evidence of complement activation and met clinical and diagnostic criteria for complement-mediated TMA [44]. These thromboses of the coagulopathy by hypercoagulation and the microangiopathy may be anticipated to be inhibited by zinc ions that zinc(10-20 mg daily) could modulate hypercoagulation and subsquent COVID-19 thrombus formation [16]. Zinc itself (1 to 3 m mol/L) induces platelet aggregation and augments aggregation induced by other agonists strengthens the view that zinc may play an important role in hemostasis, thrombosis, and atherosclerosis [45]. Thus, zinc ions may prevent COVID-19 thrombus formation and inhibit the thrombus growth for children with COVID-19 patients, causing that zinc-induced decreasing platelet count modulates the activity of coagulation protein [46].

Zinc pediatric intake may be required to be effective range 10~20 mg/d for COVID-19 prevention, 10~30 mg/d for reduction of COVID-19 bronchitis, 20~30 mg/d for recovery from COVID-19 pneumonia, and 10~30 mg/d for anti-thrombus formation and growth, in which the molecular mechanism may possess that Zn^{2+} ions could bind with viral surface proteins and thrombus protein by Zn^{2+}-centered tetrahedrally coordination pattern [47].

Thus, Zn^{2+}-induced pediatric anti-respiratory activity is enhanced and provided direct protective effects with using zinc gluconate 10 mg, zinc supplementation 30 mg/d, and zinc 15 mg ~30 mg daily with lozenges, Zn^{2+} -induced pediatric anti-pulmonary activity is enhanced for adjuvant treatment with 20 mg zinc/d, 30 mg/d of zinc supplementation with CKD. Furthermore, Zn^{2+}-induced pediatric anti-thrombotic activity is enhanced that zinc ions (Zinc 10~ 30 mg/d) could modulate coagulopathy by hypercoagulation and the microangiopathy, Zn^{2+} induced platelet-dependent fibrin formation lead to modulation of thrombus formation, Zn^{2+}-induced platelet activation enhances anti-thrombus growth, and ROS resolve venous thrombus.

Zinc-Induced Neural Thrombolytic Activity in Children

Unlike Venous thromboembolism (VTE) in older adults, an inherited hypercoagulable trait in children is rarely the only risk factor for DVT, but it does play a role in tilting the hemostatic balance and potentiating the acquired risk factors described earlier [48]. The intracardiac thrombus formation has rarely been described in the COVID-19 children patients that indicate higher thrombotic risk, in which there are hypercoagulation and acute thrombosis in patients with COVID-19 infection. Hence, conservative treatment with anticoagulation should be indicated in order to prevent subsequent hypercoagulation and thrombus formation [49]. Pediatric throm-bosis is anticoagulation that the thrombolysis can be safely performed in children but requires extensive monitoring and collaboration with hematology, critical care, and in cases of endovascular therapy and complications of thrombolytic therapy in children [50].

Enhancement of the effectiveness of thrombolytic agents with neuroprotective effects can be developed for clinical use, in which development of thrombolytic drugs are targeted on fibrinolytic agents of platelet specific agent, t-PA loading nanoparticles of red blood cells (RBCs), and RBC-tPA [51]. Zinc ions may promote neuronal thrombolysis activity that zinc-induced Cyclin-dependent kinase (CDK5) CDK5-Tyr15 phosphorylation promotes ischemic neuronal death in stroke and acute ischemic stroke is the most common type of stroke and occurs as a result of vascular occlusion [52]. Zinc-induced thrombolysis is that zinc and its chelator were showed that inhibited the thrombolytic effect significantly increased the effect of streptokinase-induced thrombolysis. Zinc chelation improves the efficiency of streptokinase in thrombolysis, accompanying with using as zinc concentration from 0.5 to 1 μM [53]. Thrombolytic drugs, namely plasminogen activators (PA), such as streptokinase (SK), urokinase plasminogen activator (uPA), tissue plasminogen activator (t-PA), recombinant tPA(rt-PA) may be used for zinc induced COVID-19 thrombolytic therapy, as the main treatment for thrombotic diseases [54]. Complications of thrombolytic therapy in children are safely performed by combination of thrombolysis/thrombectomy techniques, bleedings and anticoagulants, and benefits with hematology and critical care [5].

Zinc-Induced Covid-19 Thrombosis during ROS Production and Thrombolysis during Free Radicals Generation Resulting in Oxidative Stress

Respiratory viruses are known to induce reactive oxygen species (ROS)-generating enzymes, including nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidases, Nox) and xanthine oxidase (XO) and to disturb antioxidant defenses. ROS generation can induce cell death and the release of virions representing possible proviral role of enhanced ROS production and altered redox balance. The oxidative stress is an antiviral immune response, leading to a cytokine storm and severe inflammation, in which antioxidant supplementation is expected to ameliorate the consequences of infection [55].

Zinc induced ROS in respiratory and pulmonary COVID-19 infected cells are generated the univalent reduction of oxygen generates superoxide ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). Superoxide has an unpaired electron,

which imparts higher reactivity and renders it very unstable and short-lived. A disequilibrium between ROS generation and elimination by the antioxidant defense system results in increased bio-availability of ROS, leading to an oxidative stress. Inflammation-induced oxidative stress from injured cells could lead to irreversible cellular or tissue damage with the passage of time [56]. Thus, zinc acts as a potent agent by inhibition of ROS production and inflammation. The oxidative stress in pediatric diseases causes an oxidative burst that results in a respiratory burst and rapid ROS production, including superoxide and hydrogen peroxide [57]. However, ROS production in zinc(II)-immune pediatric patient with COVID-19 bronchitis and pneumonia cannot be elucidated yet.

ROS resolve venous thrombus in children that deep venous thrombus (DVT) formation and resolution are influenced by ROS through modulation of the coagulation, fibrinolysis, proteolysis and the complement system, and ROS induce tissue damage, thrombosis and RBC dysfunction, which contribute to COVID-19 disease severity [58]. The development of novel antioxidant treatments that aim to abrogate the formation of DVT or promote its resolution will depend on the ROS within the RBC oxidative stress, which can affect major processes involved in the development of venous thrombosis of RBC ROS in the activation of thrombotic events [59].

Zinc induced neutrophil activation and free radical generation (the most important oxygen-containing free radicals in many disease states are hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. Oxgen, hydrogen peroxide free radicals) after myocardial infarction suggest that thrombolysis does not amplify the inflammatory response and may indeed suppress it. Indeed these responses seem to be diminished and some of the beneficial effects of thrombolysis may be the result of down regulation of the acute inflammatory response [60]. Free radicals produced in living cells might result in oxidative stress, in which free radicals are produced in human body by various endogenous systems, exposure to different physiochemical conditions or pathological states displayed dominant thrombolytic action [61].

In addition, the role of zinc to pediatric vaccine plays an important COVID-19 RNA viral degradation, whether a transcriptional step may be involved in zinc-caused inhibition of vaccinia virus growth, zinc-ions at lower concentration could inhibit the infection by viral mRNAs degradation, and zinc-ions could inhibit COVID-19 by recruiting both the 5' and 3' mRNA degradation to specifically promote the degradation, including that recently COVID-19 RNA mutation could be inhibited by using Zn^{2+} ions-binding coordination pattern [62].

Zinc Ions-Binding Protein Molecular Mechanism on Anti-Thrombosis and Thrombolysis

Zinc(II) ions-induced immune antiviral molecular mechanism may be caused that Zn^{2+} ions are bound with COVID-19 molecule proteins, such as S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins of envelope virus COVID-19 by Zn^{2+} ion coordinated tetrahedrally or Zn^{2+} triad binding structure formation, leading to the formation of zinc coordinated binding proteins molecules [63]. Zn^{2+} ions-induced anti-thrombus formation and growth molecular mechanism may be resulted that Zn^{2+} could bind with coagulated protein (thrombus protein) by Zn^{2+} ions-centered tetrahedrally coordination pattern [64]. Further, zinc-binding thrombolytic molecular mechanism may be occurred that Zn^{2+} could bind with thrombolytic proteins by Zn^{2+} ions-centered tetrahedrally coodination. Thus, Zn^{2+} ions could bind with COVID-19 RNA viral surface numerous proteins, coagulated thrombus proteins and thrombolytic proteins by Zn^{2+}-centered tetrahedrally coordination pattern.

As mentioned above, Zn^{2+} ions-induced pediatric anti-viral activities for respiratory and pulmonary organs, neurological antithrom-bus formation during ROS production, and thrombolysis activity during free radicals generation against severe COVID-19 infection, and the over-all zinc binding proteins molecular mechanism on anti-thrombosis and thrombolysis, are represented in Table 1.

Table 1: Zn^{2+} ions-induced pediatric COVID-19 prevention, anti-respiratory, anti-pulmatory, neurological anti-thrombosis and thrombolytic activity, and the zinc binding coordinated proteins molecular mechanism

Zn^{2+} ions	Zn^{2+} ions-induced pediatric COVID-19 prevention, anti-respiratory, anti-pulmatory, neurological anti-thrombosis and thrombolytic activity, and the zinc binding proteins molecular mechanism				
	Prevention	**Anti-Respiratory Infection**	**Anti-Inflammatory Pneumonia**	**Anti-Thrombus Formation and Growth**	**Thrombolytic Activity**
Zn^{2+} →	→ Zn^{2+} • Zn homeostatic immune conc 3~8mg/day from 7 month, 3 year to 13 year ages • Zinc in combination with CQ/HCQ • Pediatric preventing respiratory 2019-nCoV is with zinc gluconate 10 mg • Zinc(10 to 20 mg) prevents pneumonia in children • Zinc prevents pneumonia of children 2-59 monthes • Lower Zn^{2+} conc may be efficient for vaccine candidate and higher Zn^{2+} conc may prevent respiratory ailment and acute pneumonia	→ Zn^{2+}, ($\bullet O_2^-$, H_2O_2, $\bullet OH$) • Zinc gluconate 10mg in acute lower respiratory infection • Zn (30 mg/day) in Thai children • Prophylactic zinc in infants aged 6~11 months • Zinc gluconate supplementation among children with acute lower respiratory infection • Zinc 15 mg~30 mg daily with lozenges providing direct protective effects in the upper respiratory tract.	→ Zn^{2+}, ($\bullet O_2^-$, H_2O_2, $\bullet OH$) • Adjuvant treatment with 20 mg zinc per day • Normal (80.77 + 25.3 μg/dL) • Adjuvant zinc therapy on recovery from pneumonia • Lower the serum zinc level, higher the grade of respiratory distress with children pneumonia • 30 mg/day of zinc supplementation reduces pneumonia in children with CKD • Zn + CQ/HCQ inhibit COVID-19 infection • Zinc supplements during an acute episode are not beneficial in short-term clinical recovery from severe pneumonia in hospitalized children.	→ Zn^{2+}. ROS • Zinc ions could modulate coagulopathy byhyper coagulation and the microangiopathy • Zn^{2+} induced platelet-dependent fibrin formation lead to modulation of thrombus formation. • Zn^{2+}-induced platelet activation enhances anti-thrombus growth. • ROS resolve venous thrombus • Zinc reduces neurological consequence of nervous thrombus formation and growth in pediatric COVID-19 patients.	→ Zn^{2+}. Free radicals • $ZnCl_2$ 10~50 ~ 100 μM promote streptokinase-induced thrombolysis • Zinc induced neutrophil activation and free radicals generation • Oxygen free radicals and anti-oxidative stress promote thrombolysis • Thrombolytic drugs resolve thrombosis • Zinc-induced thrombolysis drug as zinc concentration from 0.5 to 1 μM
	Zinc(II) ions-binding coordinated proteins molecular mechanism: Zn^{2+} ions may be bound with COVID-19 proteins molecules such as S(spike), E(envelope), M(membrane), and N(nucleocapsid) proteins of COVID-19 RNA respiratory and pulmonary proteins, platelet-depedent fibrin protein, blood clloting protein, thrombus protein, and thrombolysis proteins by Zn^{2+} ions-centered tetrahedrally coordinated proteins.				

Conclusions

Zinc(II) induced pediatric neurological anti-thrombosis during ROS production and thrombolysis activities during free radicals generation are discussed under the COVID-19 pandemics, and these Zn^{2+} ions-binding proteins mechanism on neurological anti-thrombus formation and thrombolysis activity has been clarified. Zinc intakes by zinc induced immunity are required 3 mg/day for 7 months to 3 years, 5 mg/day for 4~ 8 years, and 8 mg/day for 9 ~13 years in children. Supplementation have also been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the RDI for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years. The other, the normalization of Zn^{2+} intake in stroke patients with low mineral intake may enhance neurological recovery with recommended zinc neurological intake of 10 mg/day.

Zinc may reduce neurological consequences in COVID-19 patients that Zn^{2+} may promote inflammatory cytokine storms and the coronaviruses can affect the nervous system through blood circulation and cause neuroinflammation. Hence, COVID-19 in neurological disorders can present with a large increase in systemic pro-inflammatory cytokines as a neurodegenerative disorder that cause neuroinflammation.

Zn^{2+}-induced pediatric anti-respiratory activity is enhanced and provided direct protective effects with using zinc gluconate 10 mg, zinc supplementation 30 mg/day, and zinc 15 mg~30 mg daily with lozenges. Zinc gluconate supplement may result in significant reduction in respiratory morbidity among children. Zinc induced pediatric preventing respiratory 2019-nCoV is involved that specifically, supplementation with 10 mg zinc gluconate in Zn deficient children resulted in a nearly twofold reduction of the number of episodes of acute lower respiratory infections.

Zinc deficiency was very mild (3 to 5.0 mg Zn intake during the zinc-restricted period), the plasma zinc concentration remained more or less within the normal range and it decreased only after 4~5 months of zinc restriction. The other, zinc concentrations in lymphocytes, granulocytes, and platelets decreased within 8~12 weeks, suggesting that the assay of cellular zinc provided a more sensitive criterion for diagnosing mild deficiency of zinc.

Zinc induced pediatric preventing respiratory COVID-19 is required that supplementation with zinc gluconate 20 mg in Zn deficient children resulted in a nearly twofold reduction of acute lower respiratory infections. Zn^{2+}-induced pediatric anti-respiratory activity is enhanced and provided direct protective effects with using zinc gluconate 10 mg, zinc supplementation 30 mg/d, and zinc 15 mg~30 mg daily with lozenges. Zinc gluconate supplement may result in significant reduction in respiratory morbidity among children with acute lower respiratory infections. The other, preventing COVID-19 pneumonia is required that zinc

supplementation alone (10 to 20 mg) for more than 3 months significantly reduces in the rate of pneumonia and that zinc supplementation alone (10 to 20 mg), for more than 3 months, was associated with a significant reduction in the rate of pneumonia by 19%, with an RR of 0.81 (95% CI 0.73 to 0.90). Zn^{2+}-induced pediatric anti-pulmonary activity is enhanced for adjuvant 20 mg zinc/day, 30 mg/day of zinc supplementation with CKD. Adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children. 30 mg/day of zinc supplementation reduces pneumonia in children with CKD.

The thromboses of the coagulopathy by hypercoagulation and the microangiopathy may be anticipated to be inhibited by zinc ions that zinc(10-20 mg daily) could modulate hypercoagulation and subsequent COVID-19 thrombus formation. Zinc of 1 to 3 m mol/L induces platelet aggregation and augments aggregation induced by other agonists strengthens the view that zinc may play an important role in hemostasis, thrombosis, and atherosclerosis. Thus, zinc ions may prevent COVID-19 thrombus formation and inhibit the thrombus growth for children with COVID-19 patients. Furthermore, Zn^{2+} induced platelet-dependent fibrin formation lead to modulation of thrombus formation. The zinc pediatric intake may be required to be effective range 10 ~20 mg/day for 2019-CoV prevention, 10 ~30 mg/day for reduction of COVID-19 bronchitis, 20~30 mg/day for recovery from COVID-19 pneumonia, and 10~30 mg/day for neurological anti-thrombus formation and growth. And thrombolysis drug as zinc concentration from 0.5 to 1 μM may be considered.

Zinc ions may promote neuronal thrombolysis activity that zinc-induced cyclin-dependent kinase5 (CDK5) CDK5-Tyr15 phosphorylation promotes ischemic neuronal death in stroke. The ischemic brain injury develops as the result of ischemia/reperfusion with multiple mechanisms involved including inflammation, excitotoxicity, oxidative stress and apoptosis. Zinc-induced thrombolysis is that zinc, its chelator, and thrombolytic drugs were showed that inhibited the thrombolytic effect significantly increased the effect of streptokinase-induced thrombolysis. Thus, the zinc chelation specially improves the efficiency of streptokinase in thrombolysis.

Zn^{2+}-induced platelet activation enhances neurological anti-thrombus growth, and ROS(=reactive oxygen species) resolve venous thrombus. Zinc induced ROS generation and oxidative stress in COVID-19 bronchitis, pneumonia, and thrombosis in children that are caused by mRNA degradation and oxidative respiratory burst, and thrombosis revoluted by tissue damage. Respiratory viruses lead to an oxidative stress that the oxidative stress in pediatric diseases results in a respiratory burst and rapid ROS production, including superoxide and hydrogen peroxide. The other. zinc induced neutrophil activation and free radical generation such as hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical, oxgen, hydrogen peroxide free radicals suggest that thrombolysis does not amplify the inflammatory response and may indeed suppress it. The beneficial effects of thrombolysis may be the result of down regulation of the acute inflammatory response. Free radicals produced in living cells might result in oxidative stress, in which free radicals are produced in the human body by various endogenous systems, exposure to different physiochemical conditions or pathological states displayed dominant thrombolytic action.

Accordingly, zinc(II) ions-induced immune and neurological antiviral molecular mechanism on anti-thrombosis may be caused that Zn^{2+} ions are bound with COVID-19 proteins molecules such as S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins of envelope virus and coagulated thrombus proteins, leading to the formation of zinc ions-coordinated binding protein molecules. Further, Zn^{2+} ions-induced neurological thrombolysis molecular mechanism is involved that Zn^{2+} may be bound with thrombolytic proteins by Zn^{2+}-centered tetrahedrally coordinated pattern. Thus, Zn^{2+} ions could bind with COVID-19 RNA viral surface numerous proteins, coagulated thrombus proteins and thrombolytic proteins by Zn^{2+}-centered tetrahedrally coordinated pattern.

Conflicts of Interest

The author declares there is no conflicts of interest.

Sources of Funding

None

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