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COVID-19 Associated Thrombocytopenia in Children: An Emerging Issue

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Abstract

Thrombocytopenia is a risk factor for increased mortality and morbidity during the Coronavirus Disease 2019 (COVID-19). In patients with COVID-19, the mechanisms lead to thrombocytopenia seems to be multifactorial. Thrombotic consumption of platelets in microvasculature, cytokine release, sepsis, and drug induced, direct infection of megakaryocytes and autoimmune destruction of platelets are the leading etiologies in COVID-19 and thrombocytopenia. In this overview, the research was conducted by screening the relevant articles evaluating the COVID-19 associated thrombocytopenia in children. An electronic search was performed in online databases of Scopus, EMBASE, Cochrane, Web of Science and Medline (via PubMed) with English language from December 2019 up to September 2020.

Thrombocytopenia at admission in patients with SARS-CoV-2 infection is common, but delayed phase thrombocytopenia (occurring 2 weeks after beginning of symptoms) is uncertain. The delayed phase thrombocytopenia in COVID-19 is more prevalent in infected case with low lymphocyte count at admission and has a significant correlation with higher mortality rate. In majority of cases with COVID-19 and thrombocytopenia, the platelet count is mildly decreased. Severe thrombocytopenia or a prompt decline in number of platelets often indicates immune mediated thrombocytopenia or in late terminal stages of this infection. Thrombocytopenia is a significant finding in patients with severe type of COVID -19. Immune mediated platelet destruction might account for the delayed-phase thrombocytopenia in a group of patients, and can manifest as severe thrombocytopenia. It is important for practitioners to be vigilant and aware of this hematologic abnormality.

Key Words: Children, COVID-19, Immune Thrombocytopenia, SARS-CoV-2, Thrombocytopenia.

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1- INTRODUCTION

In December 2019, the outbreak of corona virus 2019 (COVID-19) was first reported in Wuhan, China, but shortly after that, this virus has become a public health emergency. (1). The lung is the principal target organ of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but this virus can affect the hematopoietic system (2). The most presenting hematologic data at admission in patients with COVID-19 is lymphopenia in 83.2% of cases and thrombocytopenia in 36.2% of them (3). In another study, Lippi et al. have been shown thrombocytopenia in 57.7% of severe COVID-19 infection, and 31.6% of patients with milder symptoms (4). In majority of cases, thrombocytopenia is usually mild and a platelet count below 100×10^9/L is unusual. Suggested mechanism for the relative preservation of platelet count during COVID-19 infection are increased thrombopoietin secretion due to liver stimulation and production numerous platelets by lung megakaryocytes (5).

In a large single center study from China on 1476 patients with COVID-19 have been documented that mortality increasing with progressively lower platelet count (6). Indeed, thrombocytopenia is a significant prognostic factor during SARS-CoV-2 infection (7). Another prognostic parameter, which can predict longer hospital stay, is platelet to lymphocyte ratio. A high platelet to lymphocyte ratio represents a cytokine storm and exaggerated platelet activation (8). Huang et al. have been demonstrated that 20% of COVID-19 infected cases who died had a platelet count less than 100×10^9/L, while only 1% of survivors (9). Severe thrombocytopenia (platelet count < 20×10^9/L) or an abrupt fall in platelet count > 50% over 24-48 hours, often indicate an immune mechanism. Furthermore, this situation could happen in the pre-terminal stages of SARS -CoV-2 infection (5). Moreover, thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (HUS) should be considered if there is associated microangiopathic hemolytic anemia (MAHA). In the case of COVID-19 associated TTP, evaluation of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) could be helpful. In this condition, the ADAMTS 13 level often drops below 10% (5). ADAMTS 13 is synthesized in the liver and its important function is to cleave von Willebrand factor (vWF) anchored on the endothelial cells and at the sites of vascular injury (10). Moreover, serial platelet count monitoring could predict the patients' outcome. Increasing number of platelet in patients with COVID-19 indicates that thrombotic process has been subsided and platelets are no longer consumed in clot.

Hence in underdeveloped countries, where access to expensive laboratory modalities is limited, clinicians should benefit from serial monitoring of platelets (11). At now, COVID-19 is a global health problem worldwide and management of COVID-19 associated thrombocytopenia has a critical importance. Severe thrombocytopenia in SARS-CoV-2 infection may cause clinical deterioration of infected cases. We aimed to review early versus delayed phase of thrombocytopenia, mechanism, pathophysiology and treatment of COVID 19 associated thrombocytopenia in this review article.

2- MATERIALS AND METHODS

In this review, an electronic search was performed in online data bases of Scopus, EMBASE, Cochrane, Web of Science and Medline (via PubMed) with English language from December 2019 up to September 2020. The single and combination keywords of: ("2019 novel coronavirus" OR "2019-nCoV" OR "COVID-19") AND (Thrombocytopenia).

The references of all included articles were searched to identify additional studies. First, two separate researchers reviewed the title and the abstracts of articles. Those studies that seemed to be related were extracted and reviewed in their full text. In the second stage, the full text of the remaining articles was carefully reviewed and articles that met the inclusion and exclusion criteria were systematically reviewed for the quality assessment. Three reviewers did this process independently and in duplication, and any disagreement was resolved by the 4th reviewer. Overall, 198 articles could be originally identified using our search criteria, 174 of which were excluded after title, abstract or full text reading, because they did not correlate with thrombocytopenia secondary to COVID-19. In this study, all review articles, cohort studies, retrospective analysis and randomized controlled trial about the main topic of article, were included. Pilot, preliminary and case report studies were not included due to limited sample size and a higher risk of bias. All studies that were not related to the subject, or were duplicate were excluded.

3- RESULTS

A total number of 24 studies were finally selected. The results of these studies have been classified in two groups: mechanisms and pathophysiology of COVID-19 associated thrombocytopenia, and treatment of thrombocytopenia secondary to COVID 19.

3-1. Early versus delayed phase thrombocytopenia

Late phase or delayed phase thrombocytopenia often occurs 14 days after symptom onset. Thrombocytopenia at admission was relatively common, however delayed phase thrombocytopenia is unclear (2). Approximately COVID-19 associated delayed phase thrombocytopenia has been detected in 11.8% of patients. It seems that late phase thrombocytopenia might be due to immune dysregulation. Moreover, this type of thrombocytopenia has a significant association with duration of hospital stay. Also it has been speculated that interleukin-6 (IL-6) has a prominent role in pathogenesis of delayed phase thrombocytopenia (2).

3-2. Mechanism of thrombocytopenia

Thrombocytopenia in patients with COVID-19 is often multifactorial. Its pathogenesis is probably more sophisticated than the conventional model of platelet consumption associated with thrombi formation in the microvasculature (5). Furthermore, COVID-19 direct invasion of bone marrow or cytokine release may lead to hemophagocytic lymphohistiocytosis (12). Another contributing factor in pathogenesis of thrombocytopenia during SARS-CoV-2 infection is the use of different drugs such as antibiotics, antivirals, heparin, azithromycin and hydroxychloroquine. (13). In majority of cases, drug induced thrombocytopenia occurs at a median of 14 days after the onset of a new drug or even sooner if there has been previous exposure.

Heparin-induced thrombocytopenia usually develops between 5 and to 10 days after the first exposure or within 24 hours of previous consumption of this drug (5). Beside drugs, some therapeutic modalities such as hemodialysis and extra corporeal membrane oxygenation (ECMO) might lead to thrombocytopenia (5). Furthermore, in patients who develop ARDS, platelet count declines, because the lung is a major site of platelet release from fully mature megakaryocytes (14). In end stage patients with multi-organ failure, thrombocytopenia may occur as a result of thromboembolism (13). In critically ill patients, thrombocytopenia often shows severe organ malfunctions and not primary hematologic etiology (15).

3-3. Pathophysiology of COVID-19 associated ITP

Immune thrombocytopenia is the most common form of acquired thrombocytopenia during childhood. The pathogenesis of ITP is complete and up to now is not exactly clear. Autoantibodies and cytotoxic $CD8^+$ T cells play a critical role in anti-platelet response leading to thrombocytopenia (16). Similar to all viral infections, SARS-CoV-2 may cause a new presentation of ITP (17) or it could trigger relapse in an existing patient (2). Moreover, ITP occur both in active phase of COVID-19 infection and up to 10 days after clinical symptoms of this novel virus subsided (13). Virus associated immune thrombocytopenia have four mechanisms (18). Firstly, the virus may cause some alteration in the host's immune system via B cell activation or release of cytokines. Second, viral agents can lead to some alterations in platelet surface proteins leading to secretion of auto antibodies against platelet glycoprotein. The third mechanism is cross reaction of virus protein directed antibodies with platelet glycoprotein. Fourthly megakaryocytes could be infected by virus and release platelets that presenting viral antigens, hence antiviral antibodies could attack against platelets (2). However, in patients with ITP, the risk of thrombosis mildly elevates (19). Moreover, this risk may be exaggerated by some therapeutic modalities in ITP such as splenectomy or thrombopoietin receptor agonists (TPO RAs). Also in presence of anti-phospholipid antibodies, the thrombotic risk highly increases. In the other hand during SARS-CoV-2 infection a hypercoagulable state occurs which may have a synergistic effect with therapeutic options in immune thrombocytopenia (5).

3-4. Treatment of COVID-19 associated thrombocytopenia

Treatment decisions during the COVID-19 pandemic depend on whether the patient is COVID-19 negative or positive. Also, treatment of ITP patients' needs a greater hospital stay and more severe immunosuppression and risks of them must be compared and balanced against the risk of bleeding from ITP (5).

3-4-1. Corticosteroids

The first line therapy for the management of new or relapsed acute ITP is prednisolone. The initial dose is often 1 mg/kg for 2 weeks and there after tapped off (20). However, World Health Organization (WHO) recommends if there are alternative treatment options, use of glucocorticoids must be avoided (21). Whether corticosteroid therapy is associated with higher risk of mortality during viral infection is not completely clear. In a recent study Arabi et al. have shown in patients with MERS (Middle East Respiratory Syndrome), use of corticosteroid had no effect on mortality but delayed clearance of MERS-CoV from the lower respiratory tract (22). However, Pavord et al. have reported in context of COVID-19, the dose and duration of treatment with corticosteroids should be kept to the minimum necessary (5).

3-4-2. Intravenous immunoglobulin (IVIG)

For immediate elevation of platelet count and also control of active bleeding, IVIG could be useful. Also in situations with failure to respond to steroid, IVIG could be useful as the second line of treatment (5). In the absence of sufficient titers of neutralizing antibodies, standard IVIG does not have a biologic effect against COVID-19 (5). However, IVIG inhibits the phagocytic function of macrophages, hence IVIG therapy especially in early stages of SARS-CoV-2 infection may be beneficial (23, 24). Moreover, in a small retrospective study from Wuhan in China have been reported that in a number of

patients with COVID-19 pneumonia, initiation of IVIG as adjunct treatment within 48 hours of admission in ICU wards, could reduce the use of mechanical ventilation, length of stay in ICU and also 28-day mortality (25). However, administration of IVIG has some important disadvantage. At first administration of IVIG needs hospitalization, secondly, supply of IVIG especially in countries with limited resources is problematic and expensive, and thirdly use of IVIG may lead to a number of systemic reactions in 5-15% of cases. Systemic adverse events can be immediate, delayed and late. In definition, immediate reactions occur within 6 hours of administration, delayed occurring 6 hours to one week after an infusion and late occurring weeks and months after infusion of IVIG. Immediate systemic adverse reaction including fever, chills and headache are often mild and controlled easily. Immediate anaphylactic reaction is rare. The most prevalent delayed systemic reaction is persistent headache. Other delayed complications such as aseptic meningitis, hemolytic reactions, renal failure and thromboembolism are uncommon, but serious and problematic (26).

3-4-3. Rituximab

Rituximab is a monoclonal antibody against CD20, which is indicated for treatment of chronic and persistent ITP (27). Administration of this drug may lead to B cell depletion and increased risk of infection, but the effect of rituximab on the risk of COVID-19 is unclear. Moreover, this drug could diminish antibody formation. Therefore, it is preferable to avoid rituximab in thrombocytopenic patients during SARS-CoV-2 outbreak (5).

3-4-4. Thrombopoietin receptor agonists

Thrombopoietin receptor agonists (TPO-RAs) are a class of platelet growth factors, which are indicated to treat ITP in both children and adults. Thrombopoietin (TPO) is the main hematopoietic growth factor, which has a key role in platelet production. Both increased platelet destruction and insufficient platelet production are responsible in ITP. Therefore, TPO-RAs such as romiplostim and eltrombopag results in an increase in platelet count in patients with immune thrombocytopenia (28). However, these drugs can take 7-14 days before an effect is seen, so in conditions which prompt elevation of platelets are needed, TPO-RAs are not suitable options and use of IVIG is indicated (5). The most significant adverse event of these drugs is the pro-thrombotic potential of them (29). Other important side effects of these drugs such as hepatobiliary adverse events and bone marrow fibrosis are not common (30). Regarding the increased thrombotic potential of TPO-RAs, administration of romiplostim or eltrombopag could result in exacerbation of thromboembolic events in patients with SARS-CoV-2 infection (5). However, in a recent systemic meta-analysis which was done on 1180 patients, have been shown TPO-RAs show a non-statistically significant trend to increase the thromboembolic events compared to controls (31). Furthermore, hepatobiliary side effects have been found to occur in 15% of patients on eltrombopag (30). Liver enzyme during treatment with eltrombopag are often elevated, therefore monitoring of liver function tests during treatment with this drug is recommended (5).

3-4-5. Immunosuppressors

Many immunosuppressant drugs including azathioprine, cyclophosphamide, cyclosporine, danazole, mycophenolate mofetil, vinblastine and vincristine have been used for treatment of chronic ITP (27).

3-4-6. Platelet transfusion

Platelet transfusions should not be routinely administered in

thrombocytopenic COVID-19 individuals with no bleeding. Transfusion of platelet concentrate can exaggerate a prothrombic state in patients with COVID-19 and coagulopathy. In immune thrombocytopenia, platelet transfusion has no value and only must be administered in life-threatening bleeding or hemorrhage in critical site such as eyes (5).

4- DISCUSSION

Outbreak of COVID-19, is rapidly spreading in all parts of world and unfortunately has unprecedented consequences for health systems and individuals alike. Thrombocytopenia is a significant hematologic finding during SARS-CoV-2 infection, which may occur at admission or late phase. In majority of cases the thrombocytopenia is often mild but immune mediated platelet destruction may lead to severe thrombocytopenia and carry a life-threatening condition. Up to now, there is not sufficient evidence about the management of COVID-19 patients with thrombocytopenia. Immune mediated thrombocytopenia may be activated during SARS-CoV-2 infection. Hence, this virus plays a critical role in the pathophysiology of COVID-19 and thrombocytopenia (32).

Marked thrombocytopenia or a prompt decline in platelet count in COVID-19 patients indicates a dismal prognosis (7). Diagnosis of COVID-19 associated immune thrombocytopenic purpura (ITP) is challenging, because many other potential causes may result in thrombocytopenia in these patients. Furthermore, SARS-CoV-2 virus can activate coagulation system leading to DIC and then thrombocytopenia (13). The main aim of treatment in COVID-19 associated thrombocytopenia is providing a safe platelet count. Steroids can be used as first line treatment in COVID-19 associated ITP, but the dose and duration of glucocorticoid administration should be decreased to the minimum necessary (5). The most important disadvantage of steroids in COVID-19 patients is inhibition of immune response and delay in clearance of virus (33). In thrombocytopenic patients with active bleeding who require a prompt elevation of platelet count, IVIG could be useful (13). Moreover, IVIG administration in early stage of COVID-19 may be useful (24). IVIG can be also used for patients who have not respond to steroids (5). TPO-RAs should be used with caution during SARS-CoV-2 infection, because these drugs may increase the risk of thromboembolic events in COVID-19 (29). As recently reported, up to 20% of hospitalized COVID-19 patients develop thromboembolism (34). On the other hand, ITP is associated with a mild increase in thrombotic risk (19). Also, this risk may be increased by specific therapeutic modalities such as splenectomy or use of TPO-RAs. Furthermore, in patients with antiphospholipid antibodies, incidence of thromboembolic events increases (5).

5- CONCLUSION

There is emerging data that COVID-19 carries a significant risk for thrombocytopenia an also thrombotic complication in infected patients. Thrombocytopenia at admission in patients with SARS-CoV-2 infection is common, but delayed phase thrombocytopenia is undetermined. Severe thrombocytopenia or a prompt decline in number of platelets often indicates immune mediated thrombocytopenia or in late terminal stages of this infection. The late phase thrombocytopenia in COVID-19 has a significant correlation with higher mortality rate. Clinicians should be aware of different mechanism leading to thrombocytopenia and proper management of this complication within COVID-19 outbreak.

6- CONFLICT OF INTEREST: None.

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