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Thrombotic Thrombocytopenic Purpura Post COVID Vaccination or TTP in COVID-19

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ABSTRACT

Background: Coronavirus disease 2019 or COVID-19 is the medical disaster that is still ongoing across the world. The disease is still evolving and changing clinical manifestations of the disease making the containment of the spread more difficult.

Summary: After seeing the constantly changing clinical manifestation of COVID-19, it is now imperative that vaccination has no alternative in the fight against COVID-19 pandemic.

Thrombocytopenia is the condition which is not common but it can be cured. But post thrombotic thrombocytopenic purpura can be dangerous. Generally the post vaccination, the adverse impact can be seen within half to one hour. But in rare cases, vaccinated persons have experience such symptoms after several hours post vaccination. The position of clots in the body may define the severity of the patients symptoms and clots in vital and sensitive area can be life threatening.

Conclusion: The rare events should not be generalized and vaccination drive should not get hampered as it is the only viable option available to contain the viral spread. More trans-boundary cohort study is needed to correlate the vaccination with any kind of adverse impact.

Key words: COVID-19, Thrombotic thrombocytopenic purpura, Thromboembolism, Vaccine hesitancy, Blood clots, Post vaccination complications

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INTRODUCTION

Coronavirus disease 2019 or COVID-19 is the evolving infectious disease which has grappled the whole world. The disease is highly infectious and spread fast from person to person. The case fatality rate associated with the COVID-19 is low as compared to other diseases but overall numbers have crossed the unfortunate mark of three million. Since its inception in Wuhan city of Hubei province in China, the disease has crossed all the geographical boundaries and spread to remotest part of the inhabitation. As of June 20, 2021, 177,967,293 infection cases and 3,853,964 case fatalities have been registered due to COVID-19 [1,2]. The figure mentioned earlier was never seen in past hundred years of human civilizational history. World Health Organization (WHO) had to declare it as the pandemic by upgrading its status from Public Health Emergency of International Concern (PHEIC) after noticing the havoc unleashed by the COVID-19. United States of America, India, Brazil, France, Turkey and Russian federation are the most affected countries [3]. The second wave has been the byproduct of the mutations in the novel Coronavirus. Public negligence in following the preventive measures is also one of the reasons behind the second and subsequent waves of COVID-19. Various vaccine candidates got approved by various drug controlling agencies around the world which has more or less same criteria and safety protocol for approval. So far 2,565,519,437 jabs have been administered all over the world of different vaccine candidates. The efficacy of the vaccine has been satisfying the criteria decided. Although events of adverse impact of the vaccine also occurred this questions the efficacy of the vaccine. Especially the occurrence of Thrombotic Thrombocytopenic Purpura (TTP) among the vaccinated population. These events are and do not cross the double digit figure. But the assessment is necessary as who vaccination drive can be in question. Certain issues are cropping up with respect to vaccination and it needs prompt attention. All these factors are comprehensively overview in this article.

LITERATURE REVIEW

Clinical manifestation of COVID-19

Novel Coronavirus also known as SARS-CoV-2 is wreaking havoc all around the world. The virus has spread to every nook and corner of the world and affected millions of people around the world. The symptoms are constantly changing and one hast to be very vigilant about its manifestation among patent. The genome sequencing revealed that the mutations that happened in the structure of the SARS-CoV-2 is making things more complicated as various anomalies in the patients are being seen [4].

The 2nd phase is partly attributed to the changes in virus structural mRNA also known as mutations that brewed in the low infection case period of the pandemic after the first phase of the pandemic. Irresponsible and negligent conduct on the part of population was also a cause behind the huge tsunami like resurgence in cases or wave of COVID-19 infection. The first wave looked lowly in front of second wave of the COVID-19 as the cases grew exponentially. Huge arrival of infected patients in outpatient department made health care infrastructure to breakdown and helpless as all the resources were under tremendous pressure. From availability of cots to oxygen cylinders and even funeral grounds were not enough to bury the people who obtain lethal clinical outcome due to COVID-19 related complications. Also unlike the first wave, this time there are huge number of post COVID-19 complications has been reported and large number of them suffered fatal blow. Long COVID-19 is already looming and people are experiencing the worst phase of the pandemic till date. The increased cases of Acute Respiratory Distress Syndrome (ARDS) made it more difficult to clinically mage the patients. Large requirements of oxygen support system was felt as high viral load among patients severe affected their lung functioning. The rapid multiplication of the virus in host also crated multi organ failure as the oxygen requirement of the body was not met by the lungs [5]. Viral load was found to be moving all over the body. The Angiotensin Converting Enzyme 2 (ACE-2) receptors which are present on vital organs like lungs, heart, kidney, liver etc. acts as a gateway for the virus. Once these organs are directly affected *via* blood then the management of the patient becomes difficult.

Comorbid patients are in worst position if they are infected. Various underlying medical conditions or comorbidities are worsening the already grim situation. Majority of the patients having any comorbidity along with COVID-19 infection needs sophisticated medical attention like ICU care and oxygen support system. Some of the severely affected individuals are ending up on ventilator support system. Lungs are the primary organs that are being affected. It is a vital organ for the proper functioning of the body as it provides oxygen to all parts of the body. Hypoxia, dyspnea is common among old aged and comorbid patients which need immediate attention. Most of them need hospitalization. The cytokine storm in which body crates a huge antibody response which results in killing normal cells of the body which are vital for living [6]. The cytokine storm is suppressed by administering the steroids like dexamethasone and other competent drug which are showing great result by suppressing immune system response. But there is a deadly consequence that has been seen in several patients discharged from the hospital and others. The occurrence of mucormycosis commonly known as black fungus due to its appearance is haunting the COVID-19 infected patients. In the first wave, the mucormycosis cases were less in number and case fatality rate was also low among patients. But in second wave the case fatality arte attached to the mucormycosis is 50-80 percent which is a serious cause of concern. Hospital acquired diabetes also saw surge in its number as undue administration of steroid made sugar levels abnormal in patients. This has resulted in occurrence of diabetes in patients who never had one prior to the COVID-19 infection. Lack of cleanliness around the patients, over administration of steroids is some of the causes behind the large number of mucormycosis patients. Almost 90-95 percent patients of mucormycosis reported diabetes mellitus which is pointing towards interesting trends. Although it is not contagious like COVID-19 but one should be cautious as it can transmit itself through intimate contact with affected person [7].

As the pandemic evolved over more than a year, the clinical manifestation among patients also changed over the course. Therefore it was necessary to reevaluate the therapeutic interventions that are in use. There has been major change in treatment course which was mandated by the circumstances and viral behavior. The hype about HCQ gone down as no key enhancement in the patient's condition or efficacy was seen among infected persons. Some of the infected persons got relief from the ailments after administration of HCQ but it was largely administered on trial and error basis. Plasma therapy was another hyped method of therapy in which the plasma component of the blood of the COVID-19 recovered patient was given to severely ill COVID-19 patients in the hope of exploiting the benefits of the antibodies of the former [8]. It was neither successfully nor failure as some of the population got relief from it. But the other factors associated were of serious nature. First there was a mental pressure on the recovered patient to donate the plasma who in most cases was severe fatigued and tired. Secondly fear of reinfection was also there due to lack of knowledge. Finally some researchers blame the plasma therapy for deadly mutations that happened and are wreaking havoc all over the world through second wave [9]. It is suspected that plasma infused in infected patients facilitated the mutations in novel Coronavirus which resulted in inception of more lethal variant. After seeing that benefits are outweighed by the harms it done, it has been discontinued as a treatment of COVID-19 in many countries. The decision was prompted by irrational and misuse of the convalescent plasma therapy which tremendously increased the pressure on blood banks. In some cases non COVID-19 was in wait to receive plasma

due to unnecessary usage in their COVID-19 counter parts [10].

Thrombocytopenia

Thrombocytopenia is the condition of low platelet count in the blood. Platelets are among four component of the blood. Other three being plasma, red blood corpuscles, white blood corpuscles. Platelets also called as thrombocytes helps in clotting the blood when any injury occurs. It stops the bleeding. In some scenario, thrombocytopenia can be totally harmless and no reaction can be seen on the affected person. However severe and critical cases of thrombocytopenia might experience bleeding from gums, teeth's etc. The healthy and expected range of platelets in the human body is 150000 to 400000. Thrombocytopenia in sine cases can be generically transmitted from parents to offspring. The causes of thrombocytopenia are various and different in different patients [11].

Vaccination and its impact on recipient

Coronavirus disease 2019 or COVID-19 is the novel disease which has struck the world in adverse way. The novelty of the disease makes the things more difficult that no medications are available in the course of treatment. Medical professional and researchers are using their experience and ad hoc measures and medicines to treat the patients which vary from patient to patient. Many medicines are repurposed for the treatment of the COVID-19.

Therefore they are in their trial stage. These medicines are not necessarily suits the patient and adverse reaction can be seen [12]. Many medicines and therapies which were said to have therapeutic impact in COVID-19 have been discarded from the treatment protocols due to their inefficacy and adverse reaction in some case. These therapies include plasma therapy, medicines include Hydroxychloroquine (HCQ), remdesivir and fabiflu has been removes from the treatment protocol as it does not serve the purpose. Occasional and conditional usages have been grated so that some of the patient can avail the benefit. Over use and administration of steroids and dexamethasone has leaded us to extremely fragile immune system. This has been explored by the microorganisms like fungus which are harmful to us. Fungus normally coexists with us and is not harmful in nature. But suppressed immunity can invite fungal infection like mucormycosis which also known as black fungus. Mucormycosis is deadly diseases which have the case fatality rate of 50 to 80 percent. If not treated in time then it can prove fatal and clinical management of the disease can be a challenge. Overuse and administration of steroids can also attract the diabetes mellitus. As uncontrolled sugar level mandates the disease. Many patients with no history of diabetes and no congenital disease are being diagnosed with diabetes mellitus which can stay for their lifetime [13]. Comorbid patients are also showing adverse and lethal clinical outcome which worsens the fight against COVID-19. A condition called long COVID-19 is persisting among population. Long COVID-19 is the condition in which the symptoms persist for long duration even after recovery too. Symptoms such as intermittent loss of taste and smell, cough cold and fever, occasional nausea and dyspnea, loss in physical capacity and weakened muscle. These conditions are present even after testing negative for the viral disease. All these can be avoided by simply following the safety and preventive measures which are given by World Health Organization (WHO) and various national agencies and health authorities. Preventive measures are way better than curative measure as it is seen in COVID-19 pandemic where whole health infrastructure collapsed in front of the huge influx of patient. Therefore it is extremely important to avoid such scenario. Vaccines are major part of the preventive strategy and are the only available viable option. Various vaccine candidates have been approved by various drug controller and approval agencies around the world and couple of phases have been completed. Initially the frontline worker such as medical professional and law enforcement agency personnel were vaccinated. Now incoming data from the follow up of the vaccinated person suggests some instances of adverse impact of vaccination which was expected from some pool of patients [14].

Especially those who are comorbid and have underlying medical illness like cardiovascular diseases, liver ailments and so on. Some of the vaccinated patients have shown such symptoms. Vaccine candidates such as Moderna, Pfizer and Oxford-AstraZeneca have been globally approved. Most of the vaccine candidates have positive results and are providing requisite protection from the viral pandemic. Cerebral venous thrombosis like life threatening conditions can be brought under control if the person is vaccinated. The danger of cerebral venous thrombosis is increased after the COVID-19 infection. In the pool of 513,284 patients examined for cerebral venous thrombosis, the chance of lethal cerebral venous thrombosis was 39 per million in non-vaccinated COVID-19 infected person and 4.1 per million people in the vaccinated people. This shows the huge benefit of the vaccination. Although rare cases have been presented with thrombotic events like blood clots and bleeding in veins. This cannot be generalized.

DISCUSSION

Thrombotic Thrombocytopenic Purpura (TTP) post vaccination

Thrombotic Thrombocytopenic Purpura (TTP) is the blood disorder in which there is formation of blood clots in the blood vessels. Low platelets and red blood corpuscles can be found in the condition which can ultimately leads to brain, kidney and damage of other vital organs. Dysfunction of some part of the organ can also be seen among certain patients.

Symptoms of TTP includes variety of them such as persisting bruises, headache, confusion, short ness of breath or dyspnea, confusion, weakness etc. Combination of above stated symptoms can be present sometimes [15]. These all are recurring and their bouts at several

times may occur. In some of the cases of TTP, the cause is traced to some points such as autoimmune disorder, certain medications which can trigger the disease, bacterial infections, pregnancy and so on. Some causes are not yet detected and their occurrence remains a topic of research. In rare cases, it can be inherited by offspring from its parent. The inheritance of TTP is also known as Upshaw-Schulman syndrome. In such cases dysfunction in enzyme ADAMTS13 (A Disintegrin and MeTallo proteinase with a Thrombo-Spondin type 1 motif, member 13) is found at birth it. Otherwise there is involvement of certain antibodies which inhibits the functioning of enzyme ADAMTS13 [16]. The subtle and non-specific symptoms and associated signs make it more difficult to diagnose it precisely. In some patients the symptoms may range from diarrhea to influenza like symptoms.

Seizures and occasional jaundice are also considered as symptoms or signs of onset of TTP. Purpura is a condition where there are sports of red or purple color which are discolored on the skin and do not changes color to white even after applying pressure. These spots are caused by injury in vessels and bleeding underneath skin occurs. This mainly happens due to low platelet count. The spots may vary from few millimeters to one centimeter. Exchange of plasma therapy happened to be a boon for the patients of thrombotic thrombocytopenic purpura as the risk associated with producing fatal clinical outcome has been dropped to 20 percent from whooping 90 percent. Timely intervention can be very effective in managing the patients of TTP [17].

In the post vaccination scenario, some patients have developed the TTP. This can create scare and can hamper the vaccination drive which is the only available and viable option to contain the pandemic. In a study one on five patients which experienced TTP post vaccination, one can find a guiding light to clear the issue properly. Severe venous thromboembolism has been found in these patients after 7 to 10 days post vaccination. Out of this, four patients had severe cerebral venous thrombosis which produces fatal clinical outcome for 3 out of them. The reason of the death of three patients was intracranial hemorrhage. The common string among all the patients was high level of antibodies to PF4 poly anion complexes. There was a sound link between thrombosis and immune system [18].

Issues with vaccines of COVID-19

Vaccination is the only arsenal available with us to contain the viral spread. Therefore it is necessary to carry out the process as soon as possible and in smooth and hassle freeway. There is a general tendency of doubting any medications that has arrived for the first time in the market. Vaccines have a long history of taking doubts on them. The trust needs to be built by competent authorities. Events like TTP among the vaccinated population can be detrimental to the vaccination efforts. Other issues are supply and demand mismatch, ambiguity in deciding the time duration between two dosages of vaccine. There is a recent study which suggested that COVID-19 infected and recovered patients must not be given preference whole vaccinating because the antibodies made by the body in response to this external pathogenic invasion are sufficient for them from protection from reinfection. It can solve the demand supply mismatch and targeted vaccination can be achieved. These people can be vaccinated in later stage of the vaccination drive [19].

CONCLUSION

Mutations or changing genomic sequence are inevitable in case of the viruses. Hence we have to be more watchful about it. Genome sequencing must be done at fixed intervals among samples from different geographical background so that all the mutations are listed and studied. The frequency of the sequencing can be increased. COVID-19 pandemic is still developing and pandemic is still far from over. The instances of Thrombotic Thrombocytopenic Purpura (TTP) are extremely rare and should not be blown out of proportion. Proper study is needed with larger pool and cross country cohort so that concrete evidence can be presented before people. Vaccine hesitancy should not gain ground among normal folks. Comorbid patients can take advices from their physician before getting vaccinated. Although there is no such requirement. The issues related to vaccination should be resolved at the earliest so that no questions remain in the mind of people before vaccinating themselves. Prevention is better than cure has been proved in COVID-19, therefore, till the issues related to vaccine of COVID-19 is not resolved, all the preventive measures must be followed with utmost sincerity.

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