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Systematic Review of Stroke Post-COVID Vaccination

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ABSTRACT

There are more than 245 million COVID-19 cases on record, and the WHO reports that approximately 5 million fatalities have been linked to the virus. Evidence of a possibility risk of stroke and other cerebrovascular issues swiftly followed the vascular and thromboembolic effects of COVID-19 that were first discovered during the epidemic. Since then, studies using comparative meta-analysis have been carried out to verify that SARS-CoV-2 infection raises the liability of ischemic stroke when compared to historical or current controls who are not infected. Apart from ischemic stroke, there have been indications of potential consequences such as hemorrhagic stroke and cerebral venous sinus thrombosis (CVST). SARS-CoV-2 vaccinations represent a major advance in the war against COVID-19. Companies and governments collaborated to develop several vaccines hostile to SARS-CoV-2 after a remarkable reaction to this worldwide disaster with destroying social, health, and economic effects. Within a year, these vaccines demonstrated noteworthy efficiency in randomized clinical studies that adapted into practical outcomes. Regretfully, following the introduction of the Ad26.COV2-S vaccine (Janssen) and the ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca), relatively few reports of thrombocytopenia and thromboembolic effects were made. This has led to a public vaccine hesitation. Nonetheless, the situation is quite complex since contamination with SARS-CoV-2 alone has a considerable hazard of thromboembolic consequences. This is particularly relevant to stroke and cerebrovascular accidents because cerebral thrombosis and hemorrhages carry a high risk of morbidity. The data about stroke and cerebrovascular problems associated with various COVID-19 vaccines is reviewed in the sections that follow. In doing so, we go over the many vaccination kinds, the physiological causes of stroke as a COVID-19 consequence, and neurological issues brought on by vaccination. In conclusion, we delineate the principal pathophysiologic anomalies and juxtapose the stroke risk associated with immunization..

Keywords: *COVID-19, Stroke, Thromboembolism, Vaccination, Cerebrovascular Complications, Thrombocytopenia*.

1. INTRODUCTION

The COVID-19 pandemic is the worst in recorded history of contemporary humanity. In below 18 months after the pandemic began, there had been four million fatalities and about 200 million confirmed cases globally.[1] The cause was found to be a unique coronavirus. Because of its high resemblance (~80%) to SARS-CoV, the unique coronavirus was determined as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV). Though it also affects other organ systems, the respiratory system is the prime victim of the SARS-CoV-2 virus. Fever, dry cough, and dyspnea were identified as symptoms associated with lower respiratory tract infections.[2] In several nations, the coronavirus infection 2019 (COVID-19) is still generating new diseases; thus, attempts to develop vaccinations that neutralize the virus and stop its transmission have intensified. Biological formulations known as vaccines offer active acquired protection against certain infectious diseases.[1] Since the COVID-19 pandemic broke out, conflicting information has been released on the prevalence of stroke in those who have the illness and the chance of SARS-CoV-2 contamination in those who have previously had a stroke.[5] Stroke is one of the primary contributors to impairment and mortality worldwide. Anti-platelet factor 4 (antiPF4) antibody may or may not be present when thrombotic thrombocytopenia is brought on by the COVID-19 vaccination.[3]. Stroke is characterized as a rapid origin localized neurological impairment of vascular origin. Stroke is the second leading source of mortality globally, yet it usually results in disability rather than death. Numerous recent investigations have recorded the possibility of stroke following COVID-19 immunization. There have been cases of ischemic, ICH, and CVST strokes, among other types.[4] Patients with Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) have previously been indicated to have stroke. There have been several reports of COVID-19 patients who have stroke problems; some of these individuals first arrived with symptoms of stroke.[6] A potentially fatal consequence of viral infection with COVID-19 is acute ischemic stroke (AIS)[5]. Treating with tPA looks reasonable for those who have both COVID-19 and stroke. As the first line of therapy, anticoagulants such as full-dosage heparin or low molecular weight heparin (LMWH) may be utilized. Human recombinant soluble (hrs) ACE2, which suppressed infection with SARS-CoV-2 in designed adult blood vessel organoids, is a prospective treatment for providing exogenous ACE2 for a more focused COVID-19 treatment.[7] For prompt diagnosis and treatment, physicians should be wary of the possibility of stroke following COVID-19 immunization [3]. After an acute ischemic stroke, post-stroke therapy is crucial to enhancing functional outcomes.[8]

2. METHODOLOGY:

DIFFERENT TYPES OF COVID-19 VACCINES

- Live attenuated vaccines
- Inactivated vaccines
- Protein-based vaccines
- Nucleic acid vaccines

i. DNA vaccines
ii. RNA vaccines

- Viral vector vaccines

i. Replicating
ii. Non-replicating

Live attenuated vaccines:

Vaccines that are live attenuated are viruses that have been weakened by passing through the cells of animals or humans until the genome mutates, making the virus incapable of causing illness. The attenuated virus induces significant B cell and T cell immune responses and replicates like a normal infection.[9] Live attenuated vaccines are naturally able to elicit TLRs (toll-like receptors) of the inbuilt immune system, which consists of CD8 T cells, B cells, and CD4 cells. Examples of these TLRs are TLR 9, TLR 7/8, and TLR 3. They can be quickly and cheaply created using "cold-adapted" viral strains, reassortments, and reverse genetics.[10] Extensive supplementary testing is necessary to verify their effectiveness and safety. Additionally, during viral replication, mutations might occur and result in recombinants after vaccination.[11]. Live attenuated vaccinations comprise those for smallpox, polio (OPV), and BCG.

Inactivated vaccines:

These are viruses that have been rendered inactive by heat or formaldehyde. They lack any living virus particle components.[11]. These are safer, more stable, and non-infectious than a live attenuated vaccination.[11] These vaccinations don't need cold chains to be distributed because they can be freeze-dried.[10] These immunizations have a subpar immunological response and don't proliferate. For greater immunogenicity, they might be used in conjunction with adjuvants.[10]. Hepatitis A and Rabies vaccines are two instances of inactivated vaccinations. One such vaccination to lessen the effects of COVID-19 is Sinovac Biotech's PiCoVacc.[9]

Protein-based vaccines:

These vaccines contain antigenic components that were created in vitro. They don't include any parts of live virus particles.[9] They are thought to be safe and to have fewer negative effects. They require numerous doses and adjuvants due to their limited immune response. It's dubious that even memory for future reactions.[10] The best antigen to produce neutralizing antibodies against the infection is the S protein of SARSCoV-2.[12] One such vaccination to lessen the effects of COVID-19 is Novavaxdies' NVX-CoV2373, which protects against the infection.[12]

Nucleic acid vaccines:

DNA vaccines:

The process of creating these vaccines involves inserting DNA into a plasmid that codes for the pathogen's antigen. Since they cannot spread illness, they are regarded as safe. There is no clinical evidence to support these vaccinations. When administered alone against the pathogen, they may result in adverse effects (ADE).[10] When combined with an inactivated vaccination, these highly immunogenic vaccines produce a strong neutralizing antibody titer.

RNA vaccines:

For RNA vaccinations, spike protein encoded by lipid-coated SARS-CoV-2 mRNA is employed. They are thought to be harmless and ineffective in inducing illness, even though they haven't been demonstrated in reality, and can cause ADE.[10]. Two such COVID-19-mitigating vaccines are BioNTech's BNT162 and Moderna's mRNA-1273 [11]

Viral vector vaccines:

Recombinant DNA science is used in the creation of these immunizations. The virus or bacteria vectors are injected with the pathogen's antigen's DNA.[9] The antigen is subsequently expressed in these cells by these bacteria or viral vectors. After being removed from the bacterium or viral vectors, the antigens undergo purification. Vaccines that use viral vectors may be replicating or nonreplicating. [10]

Replicating:

An adenovirus is genetically engineered to contain the intended gene. They can elicit a potent B cell and T cell response and are believed to be harmless. [9] Hepatitis B, HPV, and pertussis vaccinations are a few instances of these vaccines.[11]

Non-replicating:

The gene of interest is chemically modified into an unassociated virus, such as adenovirus (containing the dormant gene).[10] Although booster doses are needed to produce prolonged immunity, they are thought to be safe. Currently, these vaccinations do not have a license.[9]

3. VACCINE-INDUCED NEUROLOGICAL COMPLICATIONS:

Numerous reports of neurological problems in COVID-19 individuals have been made. While several problems manifest as general symptoms including headache, weariness, and altered mental state, there is a belief that particular neurological disorders and complications are causally linked to the infection with SARS-CoV-2.[14] Crucial modifications in both adaptive and innate immunity are brought about by infection with SARS-CoV-2. Pro-inflammatory cytokines, such as interleukins (e.g., IL-1a, IL-6, etc.), chemokines (e.g., CXCL2, CXCL1 CXCL6, etc.), and interferons (e.g., IFN-a2, IFN-2, etc.), are overproduced as a consequent[3]. In COVID-19, serum IL-6, a dependable predictor of ischemic stroke, increases.[13]

Cerebrovascular complications:

The cerebrovascular system, made up of arteries and veins, is crucial for sustaining blood flow to-and-fro of the brain.[14] The primary blood vessels that support the cerebrovascular circulation are the jugular veins and carotid arteries.[15] These blood arteries may block or burst, preventing blood supply to the brain and potentially leading to stroke that presents as neurologic impairments. [15] According to a research, five COVID-19 patients—four of them male and a female under 50—suffered strokes. These findings might point to a possible connection between the pathophysiology of stroke and COVID-19.[14] Six Italian individuals, whose average age of 69, were disclosed to experience a stroke in addition to COVID-19 in a different case series. Four patients experienced an ischemic stroke, whereas two patients experienced a hemorrhagic stroke.[16] Strokes occurred in individuals with severe COVID-19, and their prognoses were dismal. Four patients experienced organ failure, and all except one had severe pneumonia. Five patients in all passed away, and one had serious neurological impairments.[16]

Encephalopathy:

The general name for the immediate disruption of brain activity that manifests clinically as a shift in awareness is "acute encephalopathy".[14] Infections are the main cause of it, particularly those brought on by viruses.[17] Clinical features of infection with SARS-CoV-2 have been linked to many kinds of COVID-19-associated encephalopathy.[18] In a single-center longitudinal recursive analysis by Scullen and his colleagues, which comprised 76 severely sick COVID-19 patients, a total of 23 individuals showed indications of neurological involvement; 74% of the patients diagnosed with encephalopathy, and 7% of the patients with abrupt necrotizing encephalopathy.[18]

Encephalitis:

Encephalitis is a dangerous illness that causes a great deal of suffering. Viral infections account for 20–50% of encephalitis cases, with no known cause for half of those cases.[14] An encephalitis case in a female diabetic with COVID-19 age 41 has been reported. Her CSF examination revealed results that were compatible with a viral illness. Remarkably, she did not exhibit any systemic involvement or any respiratory symptoms. Instead, it was proven that she had isolated encephalitis caused by SARS-CoV-2. [19]

Subarachnoid hemorrhage:

The dangerous medical disease known as subarachnoid hemorrhage is characterized by bleeding which occurs in subarachnoid space. This subarachnoid space is situated between the pia mater, which consists of cerebrospinal fluid, and the arachnoid layer.[20] Al Saiegh et al. presented a case of subarachnoid hemorrhage in a male patient, age 31. The patient had signs of an infection related to the upper respiratory tract, slight pyrexia, arthralgia, malaise, and cough.[21] The individual lost consciousness and had an abrupt onset of acute headache. A subarachnoid hemorrhage was discovered via a head CT scan. The individual was evaluated for SARS-CoV-2 because of his respiratory problems, and the results showed that he was positive.[21]

Acute myelitis:

Zhao[22] and colleagues have described an instance of acute myelitis in a COVID-19 patient who is male and 66 years of age. The patient complained of exhaustion and fever for two days before being taken to the hospital. The patient tested positive for infection with SARS-CoV-2, and his CT scan revealed patchy abnormalities in his lungs.[22] According to Kang Zhao et al, a man of 66 years of age, from Wuhan City who had pyrexia and body pains was confirmed with acute myelitis. Patchy pneumonia was verified by a chest CT scan, and the nasopharyngeal secretion PCR resulted in a positive result for COVID-19 infection.[23]

Dizziness and headaches:

Dizziness and headaches are common yet mild symptoms of many illnesses. In many publications {23}, they have been described as mild symptoms linked to the presentation of COVID-19. Headaches and vertigo range in frequency from 3 to 12.1% {24}.

4. STROKE FOLLOWING COVID-19 VACCINATION:

A stroke can be characterized as a quickly growing condition of localized loss of brain function with accompanying signs and symptoms.[25] The symptoms don't go away after 24 hours or cause death.[25] The severity of the illness ranges from a full recovery in a single day to a severe handicap that requires lifelong care to death. There are two primary types of stroke: ischemic and hemorrhagic; the latter is more fatal than the former.[26] COVID-19 vaccinations have the potential to cause stroke in patients who have thrombotic thrombocytopenia, whether or not anti-platelet factor 4 antibody is present. Clinical attention has been drawn to the correlation between thrombosis and thrombocytopenia and a devastating clinical picture. [27] The notion of thrombosis with thrombocytopenia syndrome (TTS), also known as VITT, was developed as a result of abnormal thrombotic episodes with thrombocytopenia after COVID-19 immunization and the existence of anti-PF4 antibody. [28]

Ischemic stroke after COVID-19 vaccination:

A section of the brain loses blood supply during an ischemic stroke, which may be caused by thrombosis in an artery or a vein. After receiving the COVID-19 vaccine, thrombosis may develop in the blood vessels.[3] During the initial peak in New York City, Oxley et al. stated a number of very young individuals (less than 50 years old) who presented with major artery blockage ischemic strokes; all of these patients tested positive for infection with SARS-CoV-2.[29] People with COVID-19 who have a past experience with ischemic stroke,[30] may be due to diabetes or additional conventional risk factors for stroke, and who have greater blood levels of D-dimer seem to be at a greater risk of experiencing an ischemic stroke.[31] When it comes to the early intensity of the stroke, the results for individuals who have COVID-19 also seem to be worse.[32] SARS-CoV-2 had been demonstrated to raise the probability of atrial fibrillation, a known potential component for the ischemic type of stroke, in relation to cardiac problems.[33]

Hemorrhagic stroke after COVID-19 vaccination:

When a blood artery bursts, hemorrhagic strokes happen.[3] More research has been done on the possibility of a hemorrhagic type of stroke involving subdural, intracerebral, and subarachnoid hemorrhage.[29] According to the biggest studies conducted thus far, the frequency within hospitalized patients might be as low as 0.2%, and it was more common patients who were older and those on prophylactic anticoagulation.[34]. An independent series of cases involving 29.1 million individuals in the UK compared frequencies of COVID-19 thrombotic complications and COVID-19 vaccination rates; a positive result for SARS-CoV-2 was linked to a greater risk of CVST.[35] The transverse sinus is the primary location for over 90% of the occurrences that have been documented to have happened in women. Nonetheless, given the complex nature of the clinical presentations, it is advised to approach individuals with COVID-19, headaches, and localized neurological abnormalities with a high degree of suspicion.[29]

Cerebral venous sinus thrombosis after COVID-19 vaccination:

Young and middle-aged women are frequently affected by CVST, an uncommon kind of stroke.[3] The most typical sign of CVST is headache, which can be localized or widespread and frequently becomes worse.[36] The initial report of CVST after COVID-19 immunization came from the ChAdOx1 nCoV-19 vaccination.[37] Ad26.COV2.S, a vaccine based on adenovirus, was subsequently connected to the same occurrence, however. [37] The European Medicines Agency (EMA) reported that 34 million individuals who received the ChAdOx1 nCoV 19 vaccine may have had 169 potential instances of CVST; 54 million individuals who acquired the BNT162b2 mRNA vaccine may have had 35 potential cases of CVST; and 4 million individuals who received the mRNA-1273 vaccine may have had 5 potential cases of CVST that have not yet been vetted.[28] Out of the 7 million users of the Ad26.COV2.S vaccination, six instances of potential CVST were recorded.[38] Within four months of receiving the ChAdOx1 nCoV-19 immunization, the prevalence of CVT in those who had received the vaccination was 2.6 per million. Nonetheless, in unselected individuals, the approximated prevalence of CVT was 3–4 occurrences per million annually.[39] After the delivery of the ChAdOx1 nCoV-19 vaccination, the majority of these CVST cases were recorded. Furthermore, these individuals were vaccinated between two and twenty-four days prior to their stroke diagnosis.[3]

Vaccines responsible for different types of stroke:

i. AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine:

Thrombosis in the blood vessels might happen after receiving a COVID-19 immunization. The majority of these instances were identified after ChAdOx1 nCoV-19 was administered, particularly when the middle cerebral artery (MCA) was involved.[3] ChAdOx1 nCov-19 causes the spleen to become immune to platelets, which can lead to thrombocytopenia syndrome. Between the ages of 18 and 77 as well as between 1 and 24 days after receiving the ChAdOx1 nCov-19 vaccination, women made up the majority of stroke victims. [3] Vaccination with ChAdOx1 nCoV-19 raises the potential risk of developing ischemic stroke, which is more common than hemorrhagic stroke.

ii. Ad26.COV.2.S vaccine:

Each dosage of Ad26.COV2.S is efficient for severe-critical illness, which includes hospitalization and mortality, and can guard against both symptomatic and asymptomatic infection with SARS-CoV-2.[54] Nevertheless, compared to BNT162b2, immunization with Ad26.COV2.S was linked to a greater incidence of ischemic stroke following immunization.[55]

iii. BNT162b2 vaccine:

BNT162b2 is an mRNA vaccine modified with nucleosides and formulated in lipid nanoparticles to prevent the new coronavirus illness.[56] After 15 to 20 days following vaccination, the BNT162b2 vaccine raises the risk of ischemic stroke.[29] The BNT162b2 vaccine slightly raises the incidence of ischemic stroke compared to the chAdOx1 nCoV-19 immunization.[29]

Mechanism of vaccines causing stroke:

Comparing different COVID-19 vaccinations that cause stroke is difficult since immunization recipients differ in many fundamental ways.[3] The mechanism of thrombus development in vaccinations based on mRNA varies from vaccines based on adenovirus due to differences in manufacturing technique.[57] Compared to vaccinations with BNT162b2 and mRNA 1273, Cerebral venous sinus thrombosis (CVST) after administration with ChAdOx1 nCov-19 is more common, linked to thrombotic episodes in veins, and has a greater death toll. The medical picture of CVST after ChAdOx1 nCov-19 vaccination differs from that of CVST patients unrelated to vaccination; on the other hand, CVST following mRNA vaccinations resembles the cases which are prior to cases of COVID-19 CVST unrelated to immunization.[40] Compared to patients with cerebral venous thrombosis (CVT) after ChAdOx1 nCoV-19, individuals with CVT following Ad26.COV.2.S treatment had a higher chance of developing internal jugular vein thrombosis and intracerebral hemorrhage (ICH).[41] The two vaccinations do not significantly vary in terms of mortality or presenting symptoms such as fever, hemiparesis, headache, or visual disturbance[41]. By examining a cohort of 771,805 vaccination episodes involving 266,094 individuals, According to Pawlowski et al., there is no discernible variation in the possibility of CVST during the 30 days preceding and following the COVID-19 vaccination. [42]

Does the COVID-19 Vaccine Increase Your Risk of Stroke?

After receiving the COVID-19 immunization, your risk of stroke doesn't seem to be greater than the risk seen in the overall population. However, there seems to be a greater probability of stroke with COVID-19 infection. Numerous recent investigations have recorded the probability of stroke following COVID-19 immunization. There have been cases of ischemic, ICH, and CVST strokes, among others.[3] The majority of strokes were ischemic, and there was a rise in multiple territory infarcts and big vascular blockage, indicating a potential role for increased thrombosis and thromboembolism.[43]

What is the risk of stroke after the COVID-19 vaccine?

Studies on the prevalence of stroke following COVID-19 immunization have not stopped. Many have thus far discovered that, when compared to stroke rates in the general population, there is no rise in the frequency of stroke after receipt of the COVID-19 immunization. For instance, a 2023 research examined the risk of stroke in almost 4.1 million individuals following mRNA COVID-19 immunization. There was no increased incidence of stroke in the 28 days following immunization. This held true irrespective of age, gender, and the kind of mix of mRNA vaccinations taken.[44] According to a different analysis published in 2022, 4.7 out of 100,000 doses of the COVID-19 vaccination resulted in an ischemic stroke.[44]

COVID-19 vaccines and thrombosis with thrombocytopenia syndrome:

Rare and dangerous, thrombosis with thrombocytopenia syndrome (TTS) is a medical disease. Low levels of platelets and blood coagulation in your major blood arteries are caused by TTS. A stroke may result from these blood clots.[46] According to estimates from the Centers for Disease Control and Prevention (CDC), TTS occurs after about four million doses of the Johnson & Johnson vaccine (a viral vector vaccine).[47] A CDC advisory group declared that alternative vaccinations are favored over the J&J vaccine because of their superior safety profile, notwithstanding the rarity of TTS.[48]

Does COVID-19 raise your risk of stroke?

According to some research, having COVID-19 really raises the incidence of ischemic stroke[49] and major blood clots[50] compared to getting the COVID-19 vaccination. Having COVID-19 may raise your risk of stroke even though COVID-19-related strokes are relatively infrequent. Even in those who did not require hospitalization following their recovery from COVID-19, a greater risk of stroke may continue for several months.[51]

Is it safe to get the COVID-19 vaccine if you've had a stroke?

A history of stroke raises your chance of developing severe COVID-19;[52] however, few studies have evaluated the risk of having another stroke following COVID-19 vaccination. Therefore, in order to avoid major disease, it is advisable for stroke survivors to receive COVID-19 immunization.

What if I have stroke risk factors?

It's crucial to acquire COVID-19 immunization if you have stroke risk factors since a number of these variables are linked to an increased probability of developing a serious COVID-19 disease.[53] Older age, diabetes, smoking, sickle cell disease, high blood pressure, physical inactivity, , obesity, heart disease, and so forth are some of these risk factors.[52]

5. CONCLUSION:

Numerous recent investigations have recorded the probability of stroke following COVID-19 immunization. Intracerebral bleeding, cerebral venous sinus thrombosis (CVST), and ischemic stroke have all been reported instances. Since case reports make up most of the information about stroke after COVID-19 immunization, it is unknown with precision how often stroke occurs after COVID-19 vaccination.

Research indicates that there is no elevated risk of stroke following COVID-19 immunization when compared to stroke rates in the overall population. In actuality, obtaining COVID-19 may put you at greater risk of stroke than getting vaccinated. Individuals with an earlier history of stroke or specific stroke risk factors are at greater risk of a critical infection with COVID-19.

Finally, the public should be reassured that the immunization strategy is still the most effective strategy to prevent COVID-19 since the benefits of vaccination outweigh the danger of stroke or any other neurological problem.

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