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RESEARCH ARTICLE

COAGULATION PARAMETERS PRE AND POST VACCINATION WITH ASTRAZENECA AMONG SUDANESE POPULATION AT KHARTOUM STAT, 2022

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ABSTRACT

Background: One of four vaccinations, the AstraZeneca vaccine, was given conditional approval to prevent COVID-19. It has been licensed and approved for use in more than 170 nations, and as of late November 2021, about 1 billion doses had been given worldwide. In order to produce the SARS-CoV-2 spike protein, which triggers an immune response, the vaccine uses a unique method that relies on a chimpanzee adenovirus vector (ChAdOx).This study aimed to estimate the changes in coagulation parameters among Sudanese vaccinated with the AstraZeneca vaccine. **Materials and methods:** This was a case-control study health facility base that was conducted in the vaccine center at the institute of public health which provides vaccine services. Participants who received the first dose of the AstraZeneca vaccine were included in the study's population, along with participants who appeared to be in good health. Two groups of samples were taken before and after the immunization (the case group). Of them, 83.3% were men and 16.7% were women. Of those, 43.3% were under 30 and 56.7% were over 30.The lab work was carried out at the research lab of the Gharb El-Niel College in Khartoum. **Results:** Platelets, fibrinogen, and D.dimer showed extremely significant differences (p value 0.000) between pre- and post-vaccination in the case group.There were no appreciable differences between the pre-vaccine case group and the control group when comparing the means of the platelets count, PT, APTT, INR, fibrinogen level, and D-dimer (p value 0.05); however, when comparing the post-vaccine case group, there was a significant rise in D-dimer and a significant fall in fibrinogen level (p value 0.000). Additionally there were insignificant variations in different parameters between pre and post-vaccine groups according to gender. **Conclusion:** According to the results of this study, the first dose of the AstraZeneca vaccine significantly increased the platelets count, PT, APTT, and D-dimer levels and significantly decreased the fibrinogen levels in the Sudanese persons.

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INTRODUCTION

Corona virus disease 2019 (COVID-19) is an infectious illness brought on by the corona virus 2, a virus that causes severe acute respiratory syndrome (SARS-CoV2). In Wuhan, China, in December 2019, authorities discovered the first recorded case. The illness spread across the globe, causing the COVID-19 pandemic. [1]COVID -19 symptoms can vary, however they frequently include fever[2] cough, headache, exhaustion, breathing issues, loss of smell, and loss of taste. People can contract COVID-19 by inhaling air polluted by the virus's droplets and minute airborne particles. [3]The British-Swedish corporation AstraZeneca and the University of Oxford collaborated to create and test the corona virus vaccine ChAdOx1 nCoV-19, also known as AZD1222. A significant clinical trial revealed the vaccination provided effective protection, with a 76 percent overall efficacy. The vaccine has emergency use approval from dozens of nations, but the Food and Drug Administration has not done so yet. [4]

There are proteins embedded in the SARS-CoV-2 virus that it employs to penetrate human cells. Potential vaccinations and therapies would be a good fit for these so-called spike proteins. The Oxford-AstraZeneca vaccine is based on the genetic blueprints used by the virus to create the spike protein.The Oxford vaccine uses double-stranded DNA as opposed to the Pfizer-BioNTech and Moderna vaccines, which contain the instructions in single-stranded RNA. [5] The corona virus spike protein gene was transferred by the researchers to an adenovirus, another virus. Common viruses called adenoviruses commonly induce cold or flu-like symptoms. The ChAdOx1 chimpanzee adenovirus was modified by the Oxford-AstraZeneca team. [6] According to reports from other nations, the AstraZeneca vaccine is associated with a very uncommon but significant illness called vaccine-induced immune thrombotic thrombocytopenia (VITT), which causes blood clotting and irregular bleeding. The incidence of VITT in the general population was 1: 50,000, however this number may have been higher because the patients likely appeared before the syndrome was known, more cases

might not have been recorded, and similar cases might have been mislabeled. In general, information on the number of people immunized per decade among those under 50 years old is insufficient. According to the available data, just 8.3% of the population in Sudan had received all recommended vaccinations. The first vaccine administered to Sudanese citizens was the AstraZeneca vaccine, and there are currently no published data regarding any information for VITT syndrome and a clear gap in the hematological changes that occur after vaccination. For these reasons, this study was created to determine the changes in hematological parameters that are related to VITT syndrome.

MATERIALS AND METHODS

This was a case control study health facility base, Conducted in a vaccine centre at an institute of public health which provides vaccine services, The hematological tests were done at the research laboratory of the Gharb El-Niel College Khartoum, Sudan during the period June to September 2022.All participants attending the vaccine center at the institute of public health center , take the first dose of AstraZeneca vaccine their age is between 18-60 years ,during the aforementioned period were selected as case group. In addition to that, apparently healthy participants their age between 18-60 years who did not receive vaccine were selected as control group. Participants that had a history of bleeding, thrombi or under anticoagulant drugs or any one has been infected with corona virus before were excluded. Organized questionnaire was used for the data collection. This study was approved by the ministry of health. A written clear informed consent was obtained from all participants and explained the purpose of the research before sample collection. The participants have the right to volunteer in this research. The participant's information was saved privacy and confidentiality by using a coded questionnaire. The participant has the right to withdraw at any time without any deprivation. The participant has the right to benefit from the researcher's knowledge and skill. The investigation results were received by telephone immediately. Remaining of the blood sample wasn't reused for another study. The questionnaire was filled with the participant. From each participant, 2 venous blood were drawn from the vein using a dry sterile disposable syringe and needle. Blood samples were dispensed into sterile containers with K2 EDTA. And 1.8-2.7 ml on tri-sodium citrate anticoagulant container for APTT, PT, fibrinogen and D-dimer the samples were collected before and after vaccination; the first sample before AstraZeneca vaccine dose, and the second sample after 2-3 days of vaccination. The samples were collected by a qualified lab assistant using the protocol of the perfect sampling collection method under standardized conditions. SPSS16.0 statistical software (SPSS Inc., USA) was used for statistical analysis. Data wereexpressed as means with standard deviations (SD). A value of P <0.05 was considered statistically significant.

Procedure of coagulation tests (PT and APPT): The coagulation tests (PT and APTT) were performed using a semiautomatic device (coagulumeter).

Prothrombin time (PT) Test principle: The principle of the test consists of the use of calcium thromboplastin to measure the clotting time of the patient's plasma. The test was measured as a whole. The activity of extrinsic coagulation factors: factor XI (prothrombin), factor V (proaccelerin), factor VII (proconvertin), and factor X (Stuart factor).

Activated partial thromboplastin time (APTT) Test principle: The test involved the re-calcification of plasma in the presence of a standardized amount of platelet substitute and a specific activator. This procedure minimizes test variables by standardizing the contact activation and optimizes the concentration of platelet-like phospholipids. The APTT explores the intrinsic coagulation pathway (factors X11, X1, 1X.V111, X.V.11.1).

Platelets counts: The platelets count was done by using Sysmex Automated Hematology Analyzer KX 21N series SN B 2010.

Fibrinogen Test principle: The test was done by BioMed-Fibrinogen kite, for the quantitative determination of Fibrinogen in plasma. The principle of this kite is the addition of thrombin coagulates fresh citrated plasma, the coagulation time is proportional to thefibrinogen concentration. This allows the estimation of plasma fibrinogen by functional clotting assay.

D- dimer test Principle: The test uses the sandwich immune detection method, the detector antibodies in the buffer binds to D-Dimer antigens in the plasma sample, forming antigen-antibody complexes, and migrates through nitrocellulose matrix to be captured by other immobilized antibodies on the test strip.More D-Dimer antigens in the plasma formed more antigen-antibody complexes accumulated on a test strip which lead to a stronger fluorescence signal by detector antibodies. The signal intensity of fluorescence on detection antibody reflects the amount of antigen captured and is processed by ichroma™Reader to show D-Dimer concentration in the specimen. The working range of the ichroma™D-Dimer test is 50 – 10,000 ng/ml.

RESULTS

A total of 60 samples were collected from the Participants who took the first dose of Astra Zenecavaccine; 30 samples before the vaccination, and 30 after the vaccination (case group), in addition, 30 apparently healthy participants were selected as the control group. The frequency of the gender and age in the study; 83.3% were male and 16.7% were female, 43.3% were aged less than 30 years, and 56.7% were aged more than 30 years (Figure1,2).

Coagulation Results: In the present study the means of the controls for the platelets, PT.PTT.INR, fibrinogen and D-dimer were (268 ± 80.9),(11.4 ± 1.4), (31.1 ± 4.8),(203.3±29.5),and (4.9±1) respectively. In the case group the mean of platelets pre-vaccine was (242.1 ± 63.4), post-vaccine was (274.1± 57.6), The PT; pre-vaccine mean was (11.1 ± 1.7), post-vaccine mean was (11.4 ± 0.9),APTT; pre-vaccine mean was (32.2 ± 4.8), post-vaccine mean was (33.7 ± 6.5). The fibrinogenmean; pre-vaccine was (202.2±30.4), and post-vaccine was (195.1±29.7).D-dimer; pre-vaccine mean was (4.6±1.5), post-vaccine mean was (8.3±2) (Table 1). When comparing the parameters between pre and post-vaccine in the case group there were highly significant differences (p value ≤ 0.000*) in platelets, fibrinogen, and D.dimer (Table 2). When comparing the platelets count, PT, APTT, INR, fibrinogen level, and D-dimermeans between the control and pre-vaccine case group there were insignificant differences (p value ≥0.05), however, when compared with the post-vaccine case group there was a significant increase in D-dimer and a significant decrease in fibrinogen level(p value ≤ 0.000*) (Table 3). In addition, there were insignificant variations in different parameters between pre and post-vaccine groupsaccording to gender (Table 4). Regarding the correlation test;a significant correlation between pre and post-vaccine groups in Platelets, PT, APTT, Fibrinogen and D-dimer (p value ≤ 0.000*). (Figure3-7)

DISCUSSION

Coronavirus disease (COVID-19) is a pandemic that has been identified, and numerous vaccinations have been developed to protect against infection and the serious consequences that come with severe acute respiratory syndrome (SARS) coronavirus 2 infections. Numerous reports of sporadic post-vaccination thrombotic episodes have been made, particularly with adenovirus-based vaccinations. VATT (vaccine-associated [immune] thrombotic thrombocytopenia), VIPIT (vaccine-induced prothrombotic immune thrombocytopenia), VITT (vaccine-induced [immune] thrombotic thrombocytopenia), and

Table 1. The means of different parameters among the study population

	N	Minimum	Maximum	Mean	Std. Deviation
Platelets ($\times 10^9$/l)					
Pre- vaccine	30	139	393	242.1	63.4
Post- vaccine	30	180	400	274.1	57.6
Control	30	150	450	268.5	80.9
PT (seconds)					
Pre- vaccine	30	9.0	18.0	11.1	1.7
Post- vaccine	30	9.8	14.0	11.4	0.9
Control	30	8.0	14.0	11.4	1.4
INR					
Pre- vaccine	30	.7	2.1	1.1	0.3
Post- vaccine	30	.8	1.5	1.1	0.2
Control	30	.7	9.0	1.3	0.3
APTT (seconds)					
Pre- vaccine	30	21.6	44.0	32.2	4.8
Post- vaccine	30	19.0	42.0	33.7	6.5
Control	30	24.0	41.0	31.1	4.8
Fibrinogen					
Control	30	120	250	203.3	29.5
Pre vaccine	30	114	244	202.2	30.4
Post- vaccine	30	110	240	195.1	29.7
D-dimer					
Control (mg/l)	39	2.8	7.2	4.9	1.0
pre- vaccine(mg/l)	38	2.5	9.4	4.6	1.5
post- vaccine(mg/l)	38	5.2	15.7	8.3	2.0

Table 2. Comparison of Platelets, PT, INR, APTT, Fibrinogen and D-dimer means between pre-vaccine and post-vaccine

Parameters	Pre- vaccine (n=30)	Post- vaccine (n=30)	P. value
Platelets ($\times 10^9$/l)	242.1 ± 63.4	274.1 ± 57.6	0.000*
PT (seconds)	11.1 ± 1.7	11.4 ± 0.9	0.423
INR	1.1 ± 0.3	1.1 ± 0.2	0.739
APTT (seconds)	32.2 ± 4.8	33.7± 6.5	0.173
Fibrinogen (mg/dl)	202.2 ± 30.4	195.1 ± 29.7	0.004*
D- dimer (mg/l)	4.6 ± 1.5	8.3 ± 2.0	0.000*

Table 3. Comparison of Platelets, PT, INR, APTT, Fibrinogen and D-dimer means between control, pre-vaccine and post-vaccine

Parameters		Mean ± SD	P. value
Platelets	Pre- vaccine	242.1± 63.4	0.136
	Control	80.9 ± 14.8	
	Post- vaccine	274.1± 57.6	0.753
	Control	80.9± 14.8	
PT	Pre- vaccine	11.1± 1.7	0.470
	Control	11.4± 1.4	
	Post- vaccine	11.4± 0.9	0.954
	Control	11.4± 1.4	
INR	Pre- vaccine	1.1± 0.3	0.235
	Control	1.3± 1.5	
	Post- vaccine	1.1± 0.2	0.274
	Control	1.3± 1.5	
APTT	Pre- vaccine	32.2± 4.8	0.431
	Control	31.1± 4.8	
	Post- vaccine	33.7± 6.5	0.063
	Control	31.1 ± 4.8	
Fibrinogen	Pre- vaccine	202.2 ± 30.4	0.51
	Control	203.3 ± 29.5	
	Post- vaccine	195.1 ± 29.7	0.000*
	Control	203.3 ± 29.5	
D-dimer	Pre- vaccine	4.6 ± 1.5	0.363
	Control	4.9 ± 1.0	
	Post- vaccine	8.3 ± 2.0	0.000*
	Control	4.9 ± 1.0	

TTS have all been used to describe them (thrombosis with thrombocytopenia syndrome). Numerous findings indicate that the AstraZeneca vaccination may have an impact on certain hematological parameters, including platelet count, PT, INR, and APTT [7]. This was a case-control study health facility base, Conducted in the vaccine centre at institute of public health which provides vaccine services, The coagulation screening tests were performed at the research laboratory of the Gharb El-Niel College Khartoum, Sudan during the period June to September, 2022 to estimate the changes of coagulation parameters among Sudanese vaccinated with AstraZeneca vaccine. A total of 60 samples were collected from the Participants who took the first dose of Astra Zenecavaccine; 30 samples before the vaccination, and 30 after vaccination (case group), in addition to 30 apparently healthy participants who were selected as control group. The frequency of the gender and age in the study ; 83.3% were male and 16.7% were female, 43.3% were aged less than 30 years and 56.7% were aged more than 30 years.

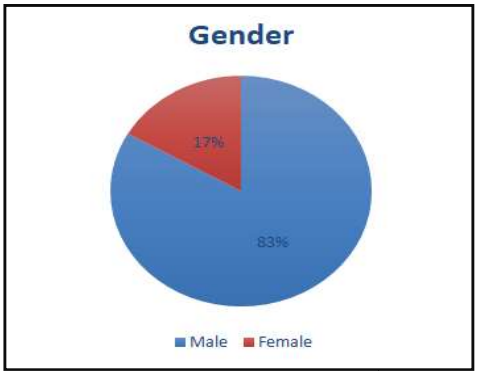

Figure 1. Distribution of gender among cases

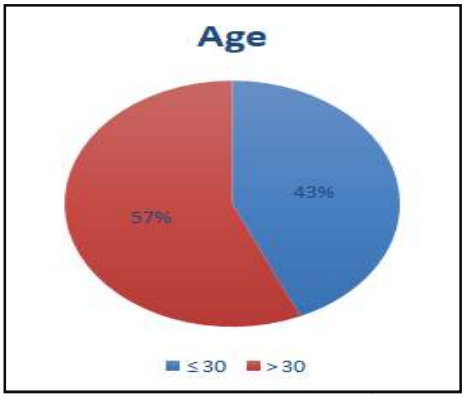

Figure 2. Distribution of age among cases

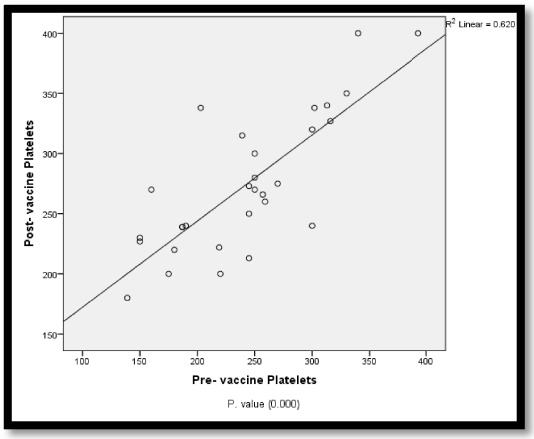

Figure 3. Correlations platelets in pre-vaccine with post-vaccine

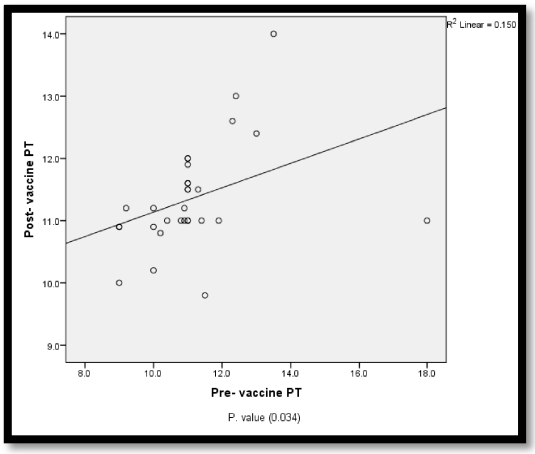

Figure 4. Correlations PT in pre-vaccine with post-vaccine

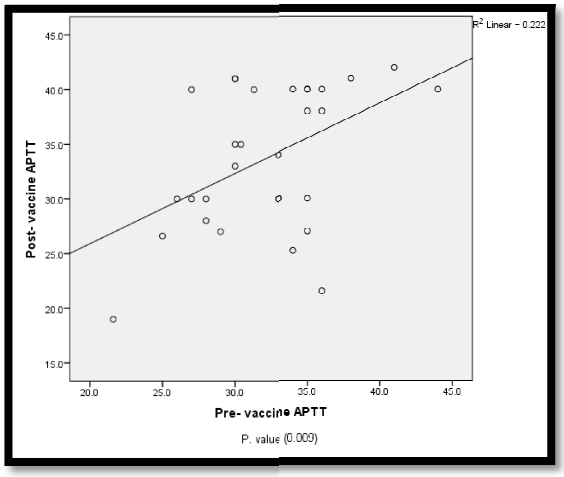

Figure 5. Correlations APTT in pre-vaccine with post-vaccine

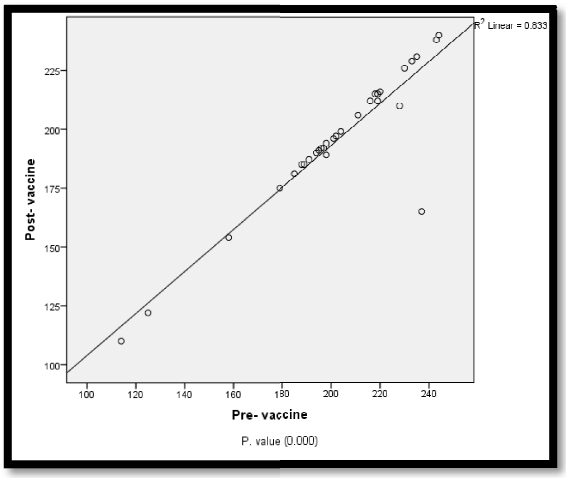

Figure 6. Correlations of fibrinogen Pre- vaccine with post vaccine

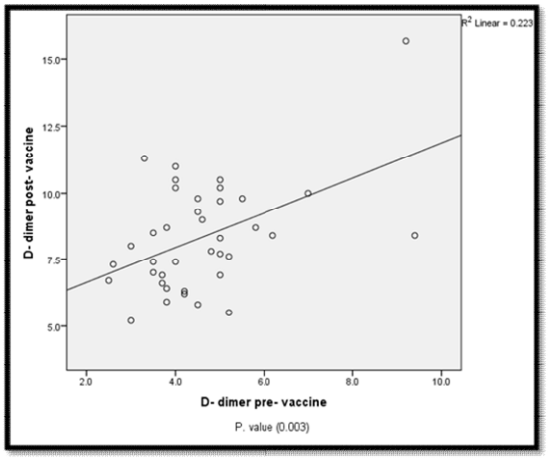

Figure (7): Correlations of d dimer Pre- vaccine with post vaccine

Additionally, the results showed that there was a highly significant rise in platelet count in the case group when comparing the Platelets mean between pre and post-vaccination. This discovery is consistent with those of LusLouren *et al*., who discovered thrombocytosis one day following the administration of the first dose of COVID-19 vaccination and microcytic hypochromic anemia (haemoglobin 7 g/L) (from AstraZeneca). [8] Other studies contradicted our findings. According to Wafa salah eldein *et al*., there was no discernible difference in platelet count between participants who had received the vaccination and those who had not. [9] In their study population, T Maryam Sharifian *et al*. similarly noted decreased platlets between 5 and 127 cells109/l[10] .

Also According to L See *et al*., the immunological thrombocytopenia caused by the vaccine occurs 2 to 5 days after the immunization [11]. Additionally, L. See *et al*. discovered that vaccine-induced immune-thrombocytopenia (VITT) occurs 2 to 5 days following vaccination [11]. Another study found that young women (aged 21 to 77) who received the AstraZeneca-Oxford vaccine 5–14 days before presentation and had thrombocytopenia in their lab results were more likely to develop VITT. [12] Also When the before and post-vaccination groups were examined in this study, the differences in PT, INR, and APTT were not statistically significant. This result was contrary to the findings of Schultz NH *et al*, who claimed that people with VITT frequently develop overtly, decompensate disseminated intravascular coagulation (DIC), which appears as normal or modestly elevated PT, INR, and APTT. [13] However, Amged Hussein *et al* findings .'s after two doses of the AstraZeneca vaccine revealed substantial differences between case and control in (PT, APTT, and INR) as well as significant differences between males and females in (PT, and APTT). [14] In the current study, there were negligible variations in the fibrinogen mean between the control and pre-vaccine case groups, but the fibrinogen level dramatically dropped when the case group was compared to the post-vaccine group. Additionally, there was a highly significant drop in fibrinogen level in the case group when comparing the fibrinogen mean between before and post-vaccination. This result was consistent with that of Fanni *et al*, who found that the patient rapidly progressed to multiple organ failure before passing away three days after being admitted to the hospital due to severe thrombocytopenia, low fibrinogen serum levels, and a marked increase in D-dimer serum levels after 13 days following the first administration of the ChAdOx1 nCoV-19 vaccine (AstraZeneca). [15] Also consistent with Luca Zazzeron *et al*'s findings, which stated that young women (ages 20 to 50) who received the AstraZeneca or Johnson & Johnson/Janssen vaccines 4-28 days previous to presentation had a higher likelihood of developing vaccine-induced immune thrombotic thrombocytopenia. While positive platelet factor 4 antibodies were consistently positive, laboratory results revealed thrombocytopenia, low fibrinogen, and elevated d-dimer levels. [16] One Australian studies showed; the platelet count is $< 150 \times 10^9$/L or falling in serial counts, D-dimer levels are elevated (five times the upper limit of normal) or fibrinogen levels are reduced to < 2 g/L. While early reports showed an over-representation of females (80%) aged 22–54 years, the Australian experience does not suggest a strong gender bias, and vigilance irrespective of age and gender is strongly recommended.[17]

Johannes Thaler *et al*. also note that thrombocytopenia, low fibrinogen, high D-dimer, and positive in the platelet factor 4/heparin-enzyme-immunoassay were seen in some individuals following administration of the ChAdOx1 nCoV-19 vaccine (AstraZeneca). [18] But according to a study by Thomas Gattringer et colleagues, laboratory tests following the initial ChAdOx1 nCov-19 (AstraZeneca) immunization showed mild thrombocytopenia (84 109/L) and noticeably raised D-dimer (14.2 mg/L; normal 0.5 mg/L). Other common markers, such as fibrinogen, were normal. [19] In this study, there were significant variations in the D-dimer mean between the control and pre-case groups, however, there was a substantial increase in the D-dimer when compared to the post-case groups. Additionally, there was a highly significant increase in D-dimer level in the case group when the mean between pre and post-vaccination was compared. This conclusion was in agreement with that of Scully M *et al*, who found that 14 out of the 23 patients in the recent British study were female. The patients were all deemed healthy and fit at the time of vaccination, and the median duration between immunization and hospital admission was 12 days. The median age was 46 years (range 6 to 24 days). Acute venous thromboembolism patients are known to have low levels of fibrinogen and highly high levels of D-dimer at presentation. None of the patients were taking heparin. [20] In general, these findings contradict those of Helene Brenna Haakonsen *et al*, who claimed that the D-dimer level was not elevated following administration of the AstraZeneca ChAdOx1 nCoV-19 vaccine. [21] The presence of EDTA in the vaccination may lead to capillary leakage and the dispersal of components in blood, according to Greinacher *et al*.

Immunoglobulin (Ig) G antibodies and the complement system detect these aggregates, which causes PF4 to cluster and activate platelets as a result. The development of neutrophil extracellular traps (NETs), which are similar to thrombocytopenia caused by heparin, is the result of cumulative responses (HIT). This results in a severe activation of the coagulation system, consumptive coagulopathy, markedly increased D Dimer levels, and hypofibrinogenemia. [21,22] Adverse reactions to the more than 600 million doses of the COVID-19 coronavirus vaccination that have been given worldwide are continuously tracked. However, in recent times there have been cases of thrombosis and thrombocytopenia occurring after vaccination with the ChAdOx1 nCoV-19 vaccine. Experimental research is required to elucidate the pathophysiology underlying VITT and potentially lower the probability of thrombosis and other adverse events happening, even though the risk of VITT is still very low and the benefits outweigh the dangers. [23] The vaccination (AstraZeneca vaccine) was connected to serious thrombotic events, with the majority of instances occurring in women under the age of 60 within 2 weeks after getting the first dose, Yasser Aladdin *et al*. mention in their conclusion. Furthermore, it was discovered that low platelet counts are typically associated with cerebral venous sinus thrombosis (thrombocytopenia). The viral proteins and free DNA in the vaccination bind to platelet factor 4 to create a neoantigen, which then triggers the production of antibodies against platelet factor 4, activating platelets and promoting clotting. This is the mechanism of thrombosis. [24]

CONCLUSION

According to the results of this study, the first dose of the AstraZeneca vaccine significantly increased the platelets count, PT, APTT, and D-dimer levels and significantly decreased the fibrinogen levels in the Sudanese persons.

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