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Sputnik V vaccine-related complications and its impression on inflammatory biomarkers in healthcare providers

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ABSTRACT

Purpose: The current pandemic made scientists create new platforms of vaccines to fight against SARS-CoV-2. Without a doubt, the new forms of present vaccines could develop a diversity of unknown complications. Sputnik V vaccine with two different adenovirus vectors (Ad26 priming and Ad5 boost) was first announced safe and effective by Russia. However, there are controversies surrounding this vaccine such as the possible decline of its immunogenicity and diminished neutralizing capacity against some Covid-19 variants. In addition, its impression on serum biomarkers is not clearly surveyed. The present study aimed to evaluate the frequency of Sputnik V vaccine-related complications and its impression on inflammatory and hematologic biomarkers.

Materials & methods: An observational cohort study was performed to evaluate the side effects and serum biomarkers changes in healthcare workers receiving Sputnik V vaccine. The vaccine adverse events were recorded daily within 60 days. The blood samples were obtained before vaccination, and on the 10th day after each dose of vaccination. The prevalence of all complications and inflammatory biomarkers levels were compared between two doses. All analyses were performed using SPSS software version 22.0.

Results: Totally, 126 participants completed the study. The mean age was 37.19 ± 7.73 years. The prevalence of all complications was higher following the first dose than the second dose. The most common side effects were pain at the injection site, body pain, fever, headache, weakness, vertigo, sore throat and sleep disorder. The hematocrit, mean corpuscular volume of red blood cells and neutrophils count declined significantly (P-value; 0.04, 0.039, 0.000 respectively).

Conclusion: It seems the side effects of Sputnik-V vaccine are mild and decrease significantly after the second dose. The decreasing level of hematocrit, MCV and neutrophil count was found significant following vaccination.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread all over the world and becoming a novel worldwide health threat [1,2]. As of April 21, 2022, there have been 505,035,185 confirmed cases of SARS-CoV-2, including 6,210,719 deaths, officially announced to WHO. This huge problem has created a heavy burden on the health system and must be controlled.

The antiviral drug remdesivir and a number of monoclonal antibodies like bamlanivimab and casirimab/imdevimab, have been officially accepted to use; but, a global vaccination against COVID-19 with the minimum side effects is indeed urgently required to terminate the
pandemic and bring life to our socio-economic activities [3,4]. In spite of the fact that the COVID-19 vaccines are immunologically effective and may prevent infections, morbidity and mortality associated with SARS-CoV2, long-term immunity and unknown complications of vaccines must still be monitored [4-7].

Various platforms are under research and development to create a highly competent vaccine against the viral infectious disease COVID-19. More than 165 COVID-19 vaccine candidates are currently being assessed around the world [8]. Results from vaccine safety monitoring efforts showed that most people have no important side effects but a few have reported serious adverse effects after COVID-19 vaccination. The current pandemic made scientists establish new platforms for vaccines, and many research are currently been developed to express the efficacy and adverse events of these vaccines. Sputnik V is an adenovirus carrier vaccine and has shown partly good cellular and humoral immune responses [9]. Even though this Russian vaccine became the first vaccine in the world to use against COVID-19 on Aug 11, 2020 [10-12], there have been substantial controversies surrounding this vaccine [11].

In Iran, COVID-19 vaccination using Sputnik-V platform started first for healthcare workers on February 2021 [13]. Although the most common complication of this vaccine was a mild flu-like condition, there were some reports demonstrating severe complications after Sputnik-v vaccine jab in Iran. For instance, Guillain-Barre Syndrome (GBS), Bell’s palsy, myocarditis, reactivation of latent herpes zoster, and severe persistent eczema have been reported in Iranian people following rAd26 and rAd5 vector-based COVID-19 vaccine administration [14-17].

In a cohort study represented by health workers immunized with the Sputnik V vaccine in Argentine, among local reactions, pain at the injection site, redness and swelling were reported 54% and 11% respectively. Among systemic reactions, muscle pain, fever and diarrhea were reported 68%, 40% and 5% respectively. Serious adverse events that required medical evaluation or hospitalization were about 5% percent [18]. They followed the candidates only after the first component of the vaccine for up to 72 h; whereas, in the current study we evaluated the participants for up to 60 days. In our study, injection site pain, and skin rash were 65.1% and 4% respectively; while, body pain, fever and diarrhea were reported 46.8%, 38.9% and 5.6% respectively.

Biochemical markers are frequently used to analyze and grading of Covid-19 disease severity in patients, but few studies focus on the impact of Covid-19 vaccine on serum biomarkers. These readily measurable serum biomarkers are reflective of inflammation after each dose of vaccination and may predict adverse reactions to the next or booster doses of vaccine.

Knowing the symptoms and complications of the vaccine candidates during a long follow-up time; as well as, knowing the changes in serum biomarkers help the researcher to deal with the adverse events of Covid-19 vaccines and prevent them in other candidates. Therefore, the aim of the present study was to evaluate the frequency of Sputnik V vaccine-related complications and its impression on inflammatory biomarkers in healthy workers at a teaching hospital.

2. Material and methods

2.1. Study design and data collection

This observational cohort study was performed at the Baharloo Hospital as a Covid referral center, between May 2021 and Sep 2021. The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethics Code: IR. TUMS.MEDICINE.REC.1399.1272; Registered Proposal Code: 51976-101-1-1400). The written informed consent was obtained from all subjects, and the study stages were explained to vaccine-receiving candidates. Besides, the participants could leave the study whenever they wanted.

Volunteers needed to carefully complete and submit their self-daily declaration forms, and also gave blood samples three times on the specified dates during the study period. In addition, PCR COVID-19 tests were done before the first and second doses of Sputnik V vaccination. Candidates' symptoms were self-reported daily for up to two months. The questionnaire included demographic data, past medical and drug history, clinical symptoms before vaccination, the past COVID infection and 19 side effects including local and systemic adverse events.

The first blood sample to measure serum inflammatory biomarkers, as a basic value, was obtained before vaccination, and the other samples were obtained on the 10th day after the first and second doses of vaccination. The aspartate aminotransferase (AST), alanine transaminase (ALT), ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), WBC, platelet count, mean corpuscular volume (MCV), and hematocrit (HCT) were determined in this regard.

Finally, the extraction results and the frequency of possible complications were obtained, and the effect of the vaccine on inflammatory biomarkers was determined.

2.2. Subjects and exclusion criteria

The participants were health care workers in Baharloo Hospital who wanted to be vaccinated with the Sputnik V COVID-19 vaccine and had negative rapid PCR Covid-19 test results on the day of immunization.

Exclusion criteria were failure to complete the adverse effect report forms, pregnancy, positive PCR COVID-19 test during the study period and uncontrolled underlying diseases.

2.3. Statistical analysis

Finally, the information recorded in the forms was entered into the SPSS software SPSS version 22.0 (SPSS Inc. Chicago, IL). Mean and standard deviation were used to describe quantitative variables and frequency and percentage were used to describe qualitative variables. To compare the means, t-test in two groups and one-way analysis of variance in more than two groups were used. Chi-square test was used to compare qualitative variables. To examine the trend of inflammatory factors, blood samples were measured three times, which were examined using trend charts.

3. Results

This study included 126 negative PCR COVID-19 participants 23–58 years of age (Mean ± SD 37.19 ± 7.73) and 85 of them were female (67.5%). Twenty-five of the participants (19.8%) had at least one underlying disease. 102 patients (81%) had no history of drug usage. Most participants (89.7%) did not have any specific clinical symptoms on the day of vaccination. One participant due to severe pneumonia unrelated to the first dose of vaccine administration, and two others because of the acquisition of Covid-19 were excluded from the study (Table 1).

Vaccine side effects were recorded daily for 30 days after each dose of vaccination. Generally, in a decrescendo pattern, injection site pain was greater in the first dose than the second dose except for paresthesia, smell or taste disorder. The prevalence of all complications was higher with the first dose than the second dose except for asthma-like symptoms which were approximately equal in both doses.

None of the participants developed visual disorders. No flu-like symptoms were reported after the first dose, and only one person developed symptoms of coryza – runny nose during the third week after the second dose. No paresthesia, smell or taste disorder was recorded after the second dose. Other details and percentages of side effects are shown in Table 2.

As shown in Table 3, the side effects after vaccination in the first dose were more common than in the second dose. The differences were statistically significant in injection site pain, headache, vertigo, weakness, body pain, sleep disorder, sore throat, cough, itching, skin rash, and Asthma-like symptoms (Table 3 and Fig. 1).
Laboratory characteristics of individuals were measured in three stages: before vaccination as a basic value (first stage) and on the 10th day after each dose of vaccine administration (second & third stages) (Table 4).

A significant decreasing trend was seen in hematocrit (HCT), mean corpuscular volume of red blood cell (MCV) and CRP titer comparing the stages. Moreover, there was a significant difference between the measured stages in respect to neutrophils and lymphocytes count. No significant differences were observed among different levels of other laboratory characteristics.

4. Discussion

Three types of Russian-developed vaccines were presented up to now. EpiVacCorona relies on synthetic peptide antigens, CoviVac works as a whole virion, and two versions of Sputnik V vaccine that act with adenovirus vectors (rAd26 and rAd5) [12]. Although none of them have met the necessary criteria for safety and efficacy by WHO until January 12, 2022, they were approved for emergency use in several Asian countries [19]. Gamaleya announced that the Sputnik V vaccine is 91.6% effective and most of the reported adverse effects were very mild. Their study was criticized by scientists worldwide in phases I and II, and also others argued the phase III data published to date [11,12]. In addition, there are some concerns about the use of Ad5-based vaccines, especially stages.
Fig. 1. Monthly percentage of the first ten side effects after the first and second doses.

Table 4
Mean ± SD of Laboratory characteristics before and after the first and second doses of vaccination in 126 study participants.

| Variables                      | Stage 1 Before vaccination (Mean ± SD) | Stage 2 After first dose (Mean ± SD) | Stage 3 After second dose (Mean ± SD) | P-value between stages 1 & 2 | P-value between stages 1 & 3 |
|--------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|-----------------------------|-----------------------------|
| AST U/L                        | 22.49 ± 5.83                          | 21.68 ± 6.97                        | 21.17 ± 8.50                        | 0.255                       | 0.085                       |
| ALT U/L                        | 22.87 ± 10.95                         | 23.72 ± 14.06                      | 21.00 ± 12.88                      | 0.485                       | 0.075                       |
| LDH U/L                        | 306.61 ± 46.59                        | 306.67 ± 58.27                     | 306.04 ± 59.72                     | 0.477                       | 0.921                       |
| Hematocrit %                   | 41.65 ± 3.39                          | 41.17 ± 3.99                       | 40.60 ± 3.73                       | 0.040                       | 0.000                       |
| MCV Fl                         | 85.32 ± 4.58                          | 84.74 ± 5.21                       | 83.51 ± 5.21                       | 0.039                       | 0.000                       |
| Platelets 10^3 count/microliter| 253.71 ± 49.71                        | 256 ± 58.59                        | 251.04 ± 59.10                     | 0.583                       | 0.524                       |
| W.B.C 10^3 count/microliter    | 7.28 ± 1.65                           | 7.11 ± 1.73                        | 7.18 ± 1.80                        | 0.254                       | 0.486                       |
| Neutrophils 10^3 count/microliter| 60.48 ± 6.25                       | 56.46 ± 8.64                      | 57.44 ± 7.73                      | 0.000                       | 0.000                       |
| Lymphocytes 10^3 count/microliter| 33.54 ± 6.15                      | 37.15 ± 7.02                      | 36.52 ± 7.53                      | 0.000                       | 0.000                       |
| Monocytes 10^3 count/microliter | 2.96 ± 0.16                           | 3.05 ± 0.67                       | 3.06 ± 0.56                       | 0.133                       | 0.051                       |
| Eosinophil 10^3 count/microliter| 3.08 ± 1.02                           | 2.93 ± 0.73                       | 2.86 ± 0.59                       | 0.196                       | 0.057                       |
| CRP mg/L                       | 4.25 ± 6.69                           | 2.70 ± 3.86                       | 2.18 ± 1.32                       | 0.027                       | 0.001                       |
| Ferritin Micro/L               | 69.51 ± 64.85                         | 82.55 ± 88.89                     | 82.44 ± 120.41                    | 0.054                       | 0.215                       |

SD: Standard deviation; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine transaminase; MCV: mean corpuscular volume of RBC; CRP: C-reactive protein.
in countries with a high prevalence of HIV-1. The application of Ad5 vector in Sputnik V vaccine against Covid-19 could raise the risk of HIV acquisition among men [11].

In our study, the injection site pain was the most common complication which was higher in the first week of the first dose, and body pain, fever, headache, and weakness were the other most common side effects after vaccination. In a study, Ghiasi et al. reported that flu-like illness, headache, fatigue and injection-site reaction were the most common side effects [20]; whereas, the flu-like symptoms were not reported in our study.

In a cohort study, 707 healthcare providers with a mean age of 35 years old vaccinated with the first component of the Sputnik V vaccine were followed up just for 72 h 71.3% reported at least one side effect. Among local reactions, 54% reported pain at the injection site, and 11% redness and swelling. Among systemic reactions, 5% reported diarrhea, 40% fever, and 68% body pain. The serious adverse events occurred in five percent of the study population that required medical support [18]. In our study injection site pain, body pain, fever, headache, weakness, and diarrhea were 65.1%, 46.8%, 38.1%, 32.5%, 29.4% and 5.6% respectively in the first week of the first dose. No serious side effects were recorded within 60 days of study time.

The FDA’s report revealed that the frequency of side effects was slightly higher after the second dose compared to the first dose [21]. Conversely, in our study, the vaccine side effects significantly decrease after the second dose in comparison with the first dose except for asthma-like symptoms, which were approximately equal following both doses. On the contrary to our results, a large prospective observational study in the UK found that systemic side effects in participants receiving Pfizer-BioNTech vaccine increased after the second dose [22]. The differences between these findings may be explained by the nature and immunogenicity of these vaccines. Further clinical research with different age groups and with larger sample sizes should be done to acknowledge our findings.

Viral invasion triggers the inflammatory response and acute phase proteins alterations may reflect the severity of the disease. Likewise, the measurement of serum biomarkers levels can be valuable to define the efficacy and highlight the safety profile of vaccines and predicts the severity of systemic reaction to the next dose of vaccine administration [23]. In the Covid-19 era, inflammatory and biochemical markers plus hematologic and cardiac biomarkers were applied for guiding appropriate therapy, predicting mortality and identifying risk stratification. On the other hand, despite the worldwide use of the different platforms of the Covid-19 vaccine, relatively little is known about its effect on the hematologic biomarkers or inflammatory markers. In a study, temporary increases in liver enzymes, increase in serum creatinine and CPK, decrease in neutrophils, increase in lymphocytes, increase or decrease in platelets have been reported after Sputnik V vaccine injection [20].

Data extracted from phase II trials for planning vaccination program done by Bhopal, showed that neutropenia occurred with AstraZeneca, BioNTech-Pfizer but not with Sinopharm, Sinovac and Johnson & Johnson. They also reported hemoglobin reduction after Novavax vaccine administration [24]. In the current study, among Sputnik V recipients, a significant decrease was seen in neutrophil count, hematocrit percentage, the mean corpuscular volume of red blood cells (MCV), and CRP titer. On the other hand, the increase in lymphocyte count was significantly different from the baseline values after the first and second doses of vaccination. Besides, the platelet count was not affected with Russian vaccination in our study.

Similarly, neutropenia was reported following the second dose among BNT162b2 mRNA Covid vaccine recipients by Sing et al. In contrast to our findings, they also revealed that lymphopenia occurred shortly after the second dose of BNT162b2 mRNA vaccination. The exact mechanism of leukopenia after viral vaccination is unclear. They argued that leukopenia events following viral vaccinations were not related to vaccine-specific effects, but a general immune response might play a role in this regard [25].

The iron metabolism and hemoglobin levels are affected in patients with Covid-19 disease. The innate immune response could limit iron availability throughout the disease to deprive the coronavirus of it, a mechanism that would be the possible cause of anemia [26]. On the other hand, the exact mechanism of decreasing HCT level and anemia following few Covid-19 vaccinations is unknown. However, autoimmune hemolytic anemia and severe aplastic anemia after SARS-CoV-2 mRNA vaccine were reported [27,28]. In addition, hemoglobin reduction following Novavax vaccine administration has also been reported recently [24]. To date, there is no study concerning Sputnik V vaccine and its impression on red blood cell profile. Interestingly, the current study revealed that Russian vaccine can induce a reduction in hematocrit and MCV following the first and second doses of vaccination.

A cohort study conducted on people receiving ChAdOx1-S/nCoV-19 vaccine showed that there was an increased risk of thrombocytopenia in the study population [29]. Other studies supported the findings that platelet count seems to be reduced in vector-based vaccines, but not in vaccines with mRNA platforms [25]. Against their suggestion, our observation provided evidence of no significant relation between platelet count and Sputnik V vaccine administration.

To the best of our knowledge, this study was the first observational study dealing with the Sputnik V vaccine side effects during 60 days, and laboratory characteristics alteration before and after the first and second doses of vaccination. We are facing several important limitations in the current study such as: the lack of comparative studies on the present topic, small sample size, and single-center research. Besides, only healthcare workers, not the general population, were enrolled in the study.

In conclusion, the finding of our study shows that the side effects of Sputnik-V vaccine appear to be mild and decrease significantly after the second dose. The decreasing level of hematocrit, MCV and neutrophil count was found significant during the study period; a new finding that should be approved by further multicentric studies.

Ethics approval

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethics Code: IR. TUMS.MEDICINE.REC.1399.1272; Registered Proposal Code: S1976-101-1-1400).

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Conflict of interest

All authors reviewed and approved the final manuscript, and report no potential conflicts of interest.

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