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Research Article

Flow Cytometric Expression of CD4 and CD8 in COVID-19 Vaccinated People in Baghdad City

Yasir W Issa[1], Shehlaa M Salih[2], Saad S Alani[3]

[1,3]Department of Anesthetic Techniques, Madenat Alelem University College, Baghdad, Iraq.
[2]Department of Biotechnology, College of Biotechnology, Baghdad, Iraq.
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I N F O

Corresponding Author:
Yasir W Issa, Department of Anesthetic Techniques, Madenat Alelem University College, Baghdad, Iraq.
E-mail Id:
yasirw.issa@mauc.edu.iq
Orcid Id:
https://orcid.org/0000-0001-5427-0602
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A B S T R A C T

Introduction: Epidemic of severe acute respiratory illness due to coronavirus (COVID-19). SARS-CoV-2 poses the greatest threat to civilisation, and an efficient vaccine plan and worldwide immunisation schedule have been introduced. This study examines the differences between vaccinated and unvaccinated individuals and the available applied COVID-19 vaccine in Baghdad, Iraq.

Method: A case-control study on 360 Iraqi volunteers involved 90 healthy controls, 90 receiving Pfizer, 90 AstraZeneca, and 90 receiving Sinopharm vaccines. The study sub-grouped cases based on follow-up after immunisation or infection status into 1 month, 2 months, and 3 months (30 each), assembling samples from vaccinated volunteers.

Results: A significantly elevated WBC count was recorded in the Sinopharm vaccinates ($p < 0.05$). Lymphocytes were highly activated in the Pfizer then Sinopharm vaccinates after one month, compared to controls. No significant differences were recorded in the monocytes among the vaccinated groups ($p > 0.05$). The granulocytes were significantly elevated in AstraZeneca vaccinates, followed by Pfizer vaccinates. Flow cytometric expression of CD4 and CD8 also showed significant increases in the vaccinated groups, there were higher CD4 and CD8 expression observed in the Pfizer, Sinopharm, and AstraZeneca vaccinates, respectively.

Conclusion: The evaluated criteria showed massive cellular immune stimulation in the Pfizer vaccinates, followed by Sinopharm, and lastly in AstraZeneca vaccinates, suggesting higher vaccine efficacy represented in Pfizer and Sinopharm vaccinates as compared to AstraZeneca vaccinates.

Keywords: Lymphocytes, CD4/ CD8, Flowcytometry, COVID-19, Vaccines

Introduction

The severe acute respiratory syndrome coronavirus 2 (COVID-19) is a newly described coronavirus illness (SARS-CoV2). Wuhan, China[1] saw the first case of the sickness in December 2019, and by January 5, 2020, the entire genome had been sequenced and published.[2] Over 6 million individuals have been infected with COVID-19 since it was designated a pandemic on March 11, 2020, with an estimated 380,000 deaths as of this writing on June 6, 2020.[3] After successful clinical testing, vaccines against COVID-19 transmission and severe disease courses become commercially accessible by the end of 2020. The spike (S) protein of SARS-CoV-24 is the antigenic target for COVID-19 vaccines because it interacts with the ACE 2 receptor on host cells, which mediates virus-cell fusion. Several types of vaccinations are currently in use, including those made from messenger RNA (mRNA), replication-incompetent vectors (RIVs), recombinant proteins, and inactivated viruses.[5] Vaccines, given in single or several intramuscular injections, stimulate the immune system to produce binding and neutralising antibodies (abs) and T cells.[6] Researchers have only extracted mRNA from the spike protein of SARS-CoV-2, even though the virus itself has 25–28 proteins. The mRNA is protected from degradation and isolation from other RNA molecules by being encased in a lipid particle.[7] To translate and code for the viral surface spike proteins important in human pathogenicity, the SARS-CoV-2 virus produces mRNA.[8] After being injected intramuscularly, this nanoparticle attaches to host cells and inserts its mRNA into the cytoplasm (rather than the nucleus) so that it may bind to ribosomes and produce viral spike proteins. The MHC-2 (antigen-presenting cells) and MHC-1-related somatic cells are two distinct protein subtypes that make it to the cellular membrane.[9] Cytokines like IL-2, IL-4, and IL5 are produced by the highly activated Th cells. The viral spike proteins are recognised by these interleukins, which trigger the differentiation of B cells into plasma cells that generate an abundance of antibodies.[10] The adenovirus in the AstraZeneca vaccine is modified chimpanzee DNA; this strain has not been introduced into human populations, and so does not elicit an immune response against the adenovirus itself but rather against the viral protein encoded in the host DNA.[11] To provoke an immunological response, the DNA vector encodes a protein like the viral s-peptide.[12] Human cells employ the DNA vector as a guide to make more chimpanzee adenoviruses and viral proteins.[13] The adenovirus from chimpanzees is injected into humans and then attaches to the host cells. The DNA leaves the nucleus and travels through the cytoplasm to the rest of the cell. It does not become part of the cellular DNA but is instead processed by host enzymes into mRNA, which then returns to the cytoplasm and engages with host cell ribosomes (either free or tethered to the endoplasmic reticulum) to produce proteins.[14] The proteins, MHC1 and MHC2, are membrane-bound complexes that are expressed on the cell membrane. T cells, B cells, plasma cells, and antibodies can all be activated by either RNA or DNA vaccines at this phase.[15] Clinical trials for Sinovac's inactivated SARS-CoV-2 vaccine incorporating aluminium hydroxide have advanced to phase 3. Phase 2 results showed that two doses of 6 g/0.5 mL or 3 g/0.5 mL of the vaccine were well-tolerated and immunogenic in healthy individuals.[16] Variable efficacy (VE) of COVID-19 vaccinations suggests that various vaccines may produce distinct immunological memories. Multiple obstacles have prevented thorough analyses of how various COVID-19 vaccines fare regarding immunogenicity and immunological memory. To begin, consistent cellular tests that allow for direct comparisons between treatments are typically absent. Using World Health Organization (WHO) worldwide standards, the quantity of binding and neutralising antibodies may be measured consistently.[17] Quantitative comparisons are needed to measure memory T and B cells within the same research since the use of live cells and sophisticated reagents makes CD4+ T cell, CD8+ T cell, and memory B cell assays less transferable between laboratories. A prime example of this is the incongruity between studies looking at CD8+ T cell responses to COVID-19 mRNA vaccines; early reports suggested significantly different CD8+ T cell response rates to BNT162b2 compared to mRNA-1273.[18] Second, the dynamics of vaccine-specific immunological memory in people must be studied longitudinally using cryopreserved PBMCs. Furthermore, few studies have evaluated vaccination responses in terms of antibodies, CD4+ T cells, CD8+ T cells, and memory B cells in the same people. By tracking cellular immune responses in infected and vaccinated participants, this study attempted to assess the efficacy of currently available vaccinations in Iraq.

Materials and Methods

Subjects

A case-control study was conducted on 360 Iraqis who participated; 90 subjects served as healthy controls for the case-control design, The inclusion criteria were that 90 received the Pfizer vaccination, 90 subjects received the AstraZeneca vaccine, 90 subjects received the Sinopharm vaccine, all studied cases were sub-grouped according to follow up after immunisation status into 1 month, 2 months and 3 months. Their age ranges were 22 to 65 years and their age matched 90 healthy individuals and their age range was 22–55 years. The exclusion criteria were those out of 3 months follow-up, with previous history of chronic illness. The study was approved by the Ethics Committee of the College of Biotechnology, Al-Nahrain University. Consent was taken from patients for inclusion in the study. The samples were collected from different hospitals in Iraq

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including Baghdad Teaching Hospital, AL-Forat General Hospital, and Ibn AlKateeb Hospital, Baghdad, Iraq during May 2020–April 2022. Samples were also collected from healthy vaccinated volunteers from Al-Zawiya, Bab Al-Muadham, Al-Yarmouk, Alrasheed, Al-Bayaa, Al-Mahmodia, and Al-Saydia Health Centers, Iraq.

Samples Collection and Cell Staining

Three ml of venous blood was collected from forty subjects after three months of infection and vaccination, The aliquot was dispensed in an EDTA Tube for CBC and Flowcytometry test. Up to 5 µl, of each fluorescently labelled monoclonal antibodies (CD4 and CD8) were added to 100 µl of whole blood and then incubated for 15 minutes. Then 2 ml of cell lysis was added to the mixture and set for 10 minutes in the dark (drawer). The mixture was centrifuged at 1792 g for 5 minutes. The washing step was carried out with 2 ml of cell wash (buffer) to the mixture then centrifuged at 1972 g for 5 minutes and discarded and repeated two times. Finally, up to 500 µl of cell sheath was added to the pellet and read by flow cytometry.

Statistical Analysis

The software GraphPad Prism 8 was used to obtain the mean and SE, and values with $p < 0.05$ were considered statistically significant.

Results

Distribution of Subjects According to Age and Gender

Age and gender distributions are shown in Table 1. There were significant differences between the frequency of males and females recorded ($p = 0.000$).

Total and Differential Leukocyte Count

Analysis of variance showed that there was a significant increase in total WBC count ($p < 0.05$) in the first month of Sinopharm vaccinates (12.12 ± 1.21). There was also a dramatic increase in lymphocyte count followed 1st month in Pfizer (34.4 ± 5.89%) and Sinopharm vaccinates (33.33 ± 4.5%). There were no significant differences in monocytes detected in the vaccinated individuals compared to the control. Analysis of variance recorded a significant increase in granulocyte count in AstraZeneca vaccinates (68.2 ± 7.32%), then Pfizer (65.1 ± 4.62%) (Table 2).

CD4+ and CD8+ Flow Cytometric Expression in Vaccinated Groups

The results of vaccinated subjects after 3 months followed immunisation showed a significant elevated in the total lymphocyte count in the Sinopharm (303.32 ± 6.3 cells/ul), as well as Pfizer vaccinated groups (264.56 ± 8.1 cells/ul) compared to control (197.37 ± 4.3 cells/ul) ($p < 0.05$), while no significant differences recorded in AstraZeneca vaccinated group (189.78 ± 5.2 cells/ul), ($p > 0.05$).

The results showed significant differences in the flow cytometric expression of CD4 in the vaccinated groups compared to controls. There was significant elevation expression of CD4 was recorded in the Sinopharm (12.5 ± 2.1%) and Pfizer vaccinated groups (10.9 ± 2.1%), otherwise there were significant drops in AstraZeneca vaccinated group in the CD4+ T cells (5.98 ± 1.3%). The results also showed significant differences in flow cytometric expression of CD8 in the vaccinated groups, there was a significant elevation in the Pfizer groups (10.6 ± 2.9%), followed by Sinopharm vaccinated groups (9.7 ± 2.1%), and there was a significant drop in the AstraZeneca vaccinated group (5.85 ± 1.7%) (Table 3 and Figure 1).

Table 1.Distribution of Vaccinated Subjects and Control According to Age and Gender

Groups	No. of Cases	Age (Years) Mean ± SE	Male n (%)	Female n (%)
Control	90	37.12 ± 2.87	60 (60)	30 (40)
Pfizer vaccinate	90	47.43 ± 8.35	55 (61)	35 (39)
Astra-Zeneca vaccinate	90	33.64 ± 7.05	58 (64)	32 (36)
Sinopharm vaccinate	90	27.43 ± 4.21	64 (71)	26 (29)

Table 2.Total and Differential Leukocyte Count (Mean ± SE) in Vaccinated Groups After 3 Months of Vaccination

Groups	Duration (Months)	N	WBC (Mean ± SE) ($10^{\wedge 9}$/L)	Lymphocytes (Mean ± SE) %	Monocytes (Mean ± SE) %	Granulocytes (Mean ± SE) %
Control	0	90	5.98 ± 2.44[a]	28.21 ± 4.32[a]	9.78 ± 3.44[a]	48.99 ± 4.33[a]
Pfizer	1	30	7.04 ± 2.33[a]	34.4 ± 5.89[b]	9.5 ± 2.33[a]	65.1 ± 4.6[2]b
	2	30	6.763 ± 3.11[a]	31.56 ± 6.11[a]	9.93 ± 2.45[a]	58.5 ± 6.32[a]
	3	30	7.41 ± 1.54[a]	28.26 ± 3.15[a]	9.16 ± 2.01[a]	58.67 ± 4.23[a]

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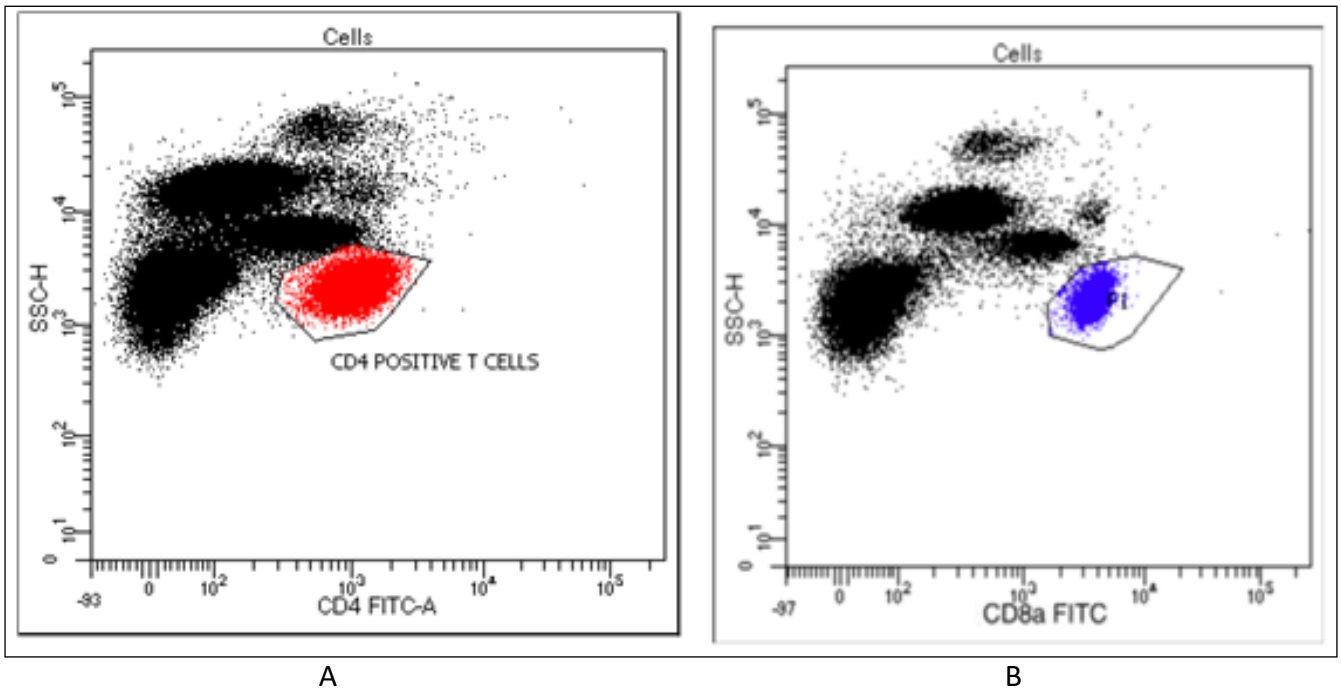
AstraZeneca	1	30	9.1 ± 3.35[a]	28.95 ± 4.66[a]	8.3 ± 2.331[a]	68.2 ± 7.32[b]
	2	30	8.24 ± 2.87[a]	30.1 ± 4.87[a]	8.7 ± 1.21[a]	61.2 ± 5.63[b]
	3	30	6.8 ± 2.37[a]	23.8 ± 3.02[a]	10.4 ± 2.33[a]	56.8 ± 6.52[a]
Sinopharm	1	30	12.12 ± 1.21[b]	33.33 ± 4.[5]b	6.7 ± 3.01[a]	56.4 ± 2.01[a]
	2	30	11.62 ± 1.05[a]	25.3 ± 4.12[a]	6.23 ± 1.33[a]	53.13 ± 3.31[a]
	3	30	7.82 ± 1.88[a]	31.11 ± 1.98[a]	7.56 ± 2.71[a]	54.32 ± 1.33[a]
Probability			0.001**	0.001**	0.612 NS	0.000**
Different letters in columns represent significant differences; NS: Non-significant; **: Significant (p < 0.01)						

Table 3.Flow Cytometric Expression of CD4 and CD8 in Vaccinated Groups After 3 Months of Vaccination

Groups	N	Lymph (Mean ± SE) %	Lymph (Mean ± SE) Cells/ul	CD4 (Mean ± SE) %	CD4 (Mean ± SE) Cells/ul	CD8 (Mean ± SE) %	CD8 (Mean ± SE) Cells/ul
Control	40	28.210 ± 4.600[a]	197.370 ± 4.300[a]	6.500 ± 1.100[a]	1241.405 ± 6.300[a]	6.400 ± 1.000[a]	1226.768 ± 4.200[a]
Pfizer	40	33.780 ± 5.200[a]	264.560 ± 8.1[b]	10.900 ± 2.100[b]	2858.710 ± 12.200[b]	10.600 ± 2.900[b]	3017.780 ± 9.400[b]
Astra-Zeneca	40	28.380 ± 3.600[a]	189.780 ± 5.200[a]	5.980 ± 1.300[a]	1064.780 ± 7.100[b]	5.850 ± 1.700[a]	1038.420 ± 5.300[b]
Sinopharm	40	30.530 ± 4.100[a]	303.320 ± 6.300[b]	12.500 ± 2.100[b]	3776.960 ± 6.300[b]	9.700 ± 2.100[b]	2931.480 ± 8.200[b]
Probability		0.088 NS	0.041 *	0.012 *	0.000 **	0.001 **	0.001**

Different letters in columns represent significant differences; NS: Non-significant; **: Significant (p < 0.01)



A B

Figure 1(A).CD4+ T Cell (B).CD8+ T-cells Population in the Vaccinated Groups

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Discussion

COVID-19 vaccinations have shown promising results in clinical studies, protecting against viral transmission and severe illness.[19] Two doses of the COVID-19 vaccine appear to be sufficient for a strong lymphocyte-specific antibody and T-cell response in healthy individuals. Vaccination effectiveness discussions must consider variations in vaccine safety profiles. The claimed effectiveness of RNA and DNA vaccines is significantly higher than 95%, compared to that of other vaccination platforms. Inactivated vaccinations were found to have a 78.1% success rate against BBIBP-CorV and a 50.7% success rate against. Vaccines were 69% effective against COVID-19 when given 14 days prior to the beginning of symptoms.[20] Studies have shown that after COVID-19 vaccination, lymphocyte counts rise, and one research has shown that SARS-CoV-2 may directly infect macrophages as well as CD4+ and CD8+ lymphocytes.[21] The failure of SARS-CoV-2 infection in human monocyte-derived DC and macrophages in vitro was confirmed by additional independent infection experiments, which also confirmed the induction of antiviral and proinflammatory cytokines such as IFN-/, TNF, IL-1, IL-6, and IL-10, and CXCL10, which ultimately resulted in type I IFN-mediated host cell death.[22] An additional investigation validates our findings by showing that following the identification of SARS-CoV-2, monocytes, and macrophages undergo metabolic changes that lead to the stimulation of inflammatory pathways.[23] According to in vitro studies using antigen stimulation of CD4+ T cells, an increase in innate cells will generate powerful T cell responses, with a peak around day 14. Different protective mechanisms may thus be apparent after one compared to two doses of this vaccine, despite identical effectiveness after one and two doses. T-cell responses are reduced after the second dose while antibody responses are raised. Vaccine immunogenicity and effectiveness were found to improve with longer intervals between doses.[24] Our findings were also confirmed by recent studies in the field of evaluation of COVID-19 vaccine effectiveness and reported the efficacy of Pfizer vaccines and Sinopharm than AstraZeneca vaccine.[25–27] Clinical tests have demonstrated that COVID-19 vaccinations are highly effective at reducing viral transmission and severe illness courses.[28] Consequently, it appears that non-immunocompromised individuals have a significant antibody and T-cell response following two doses of COVID-19 immunisation. Vaccine safety profiles must be evaluated within the context of their effectiveness. The claimed effectiveness of RNA and DNA vaccines is 95% greater than that of other vaccination platforms. The effectiveness of inactivated BBIBP-CorV vaccines was reported to be 78.1% and 50.7%, respectively.[29] Vaccines were 69% effective against moderate to severe critical COVID-19 with an onset at least 14 days after injection Numerous studies reported the elevation of Lymphocytes following COVID-19 infection and vaccination, and a study reported Direct infection of macrophages and CD4+ and CD8+ lymphocytes with SARS-CoV-2.[30] Additional independent infection experiments confirmed the abortive SARS-CoV-2 infection in human monocyte-derived DC and macrophages in vitro and corroborated the induction of antiviral and proinflammatory cytokines, including IFN-α/β, TNF, IL-1β, -6, and -10, as well as CXCL10, leading to type I IFN–mediated host cell death.[31,32] A study confirms our results by elevation of lymphocytes and granulocytes that allowed induction of inflammatory pathways in monocytes and macrophages upon recognition of SARS-CoV-2, metabolic alterations in these cells have been reported.[33] Increases of innate cells will induce potent T cell responses that peaked at 14 days after a single dose, based on the production of TNF and IFNγ from CD4+ T cells upon antigen stimulation in vitro. The similar efficacy after one and two doses of this vaccine, despite decreased T cell responses and increased antibody responses after the second dose, suggests that different protective mechanisms may therefore be prominent after one compared with two doses. Increased immunogenicity and efficacy were observed with increasing intervals between doses for the vaccines.[34] Other studies reported the lower lymphocytes and higher neutrophils following infection could be used as a diagnostic marker for COVID-19 infection.[35] Thus, could explant the viral progression or genotyping variations following vaccination, and the elevated lymphocytes and granulocytes following the 1st month of infection might probably be in responses to cytokines characterised by markedly increased levels of interleukins and TGF-β, FGF, and other factors which may promote lymphocyte development at the recovery situation.[36]

Conclusion

The study showed massive cellular immune stimulation in the Pfizer vaccinates, followed by Sinopharm, and lastly in AstraZeneca vaccinates, suggesting higher vaccine efficacy in Pfizer and Sinopharm vaccinates as compared to AstraZeneca vaccinates.

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