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D-Dimer Rise: A Possible Link with COVID-19 Vaccines?

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Abstract

This observational prospective study was conducted on 17 4-shots COVID-19 vaccinated patients who came for a primary consultation. The aim of the study was focused on coagulation biomarkers. The platelet count and D-dimer level were the numeric parameters studied. The study showed a minor decrease of the platelet count in 2 patients (12 %). Conversely, we observed an abnormal elevation of D-dimer levels in 12 patients (71%).

In conclusion, this preliminary study on 4-shots COVID-19 vaccinated patients suggests a possible link between a rise in D-dimer and COVID-19 vaccines. Hopefully, it was not correlated with any thrombotic events or prolonged bleeding, but it deserves careful investigation to be sure that this biological alteration is not durable and deleterious.

Keywords: *SARS-CoV-2, COVID-19 Vaccines, Booster, Platelet Count, D-Dimer.*

INTRODUCTION

Since the introduction of COVID-19 vaccines, data on the possible side effects collected worldwide have been described and can be easily consulted on open data base such as Open VAERS. It is now recognized that these adverse reactions can affect clinically all the organs, but surprisingly biological alterations have received less interest. Within these biological alterations, most are related to coagulation disorders. For this reason, we now systematically include a coagulation blood test for COVID-19 vaccinated patients before surgery. Thus in a previous study, we have detected an abnormal rise of the D-dimer in 2 or 3 shots vaccinated patients; however the relationship with COVID-19 vaccines is not clear because we treat mainly in our office aged patients with comorbidities that can modify the D-dimer titer [1]. Nevertheless, we are now dealing more frequently with multiple vaccinated patients (with 4 dose and sometimes 5 dose vaccinated patients) and we have extended our study to this new population to determine if repeated injections could induce more frequent bloods disorders.

MATERIAL AND METHODS

This observational prospective study was conducted on a cohort of 17 patients having a full vaccination regimen with four COVID-19 doses. This included 11 males and 6 female. The ages ranged from 59 to 88 years old (mean: 75 years). Among these vaccinated patients, 4 had an heterologous vaccination scheme (one with Astra Zeneca and Comirnaty, three with Moderna and Comirnaty). All other vaccinated patients received four doses of Comirnaty vaccines. In their medical history, 5 had diabetes, 5 had cardiopathy (3 coronary diseases, one cardiac valvulopathy, one atrial fibrillation), 2 had inflammatory diseases (one erysypelas, one Cogan syndrome), one patient had a brain trauma with epileptic seizures and one patient had a breast cancer in remission. Two out of 17 patients reported having been tested positive for COVID-19 after the second and third dose of Comirnaty vaccines. Another one presented a Zoster thoracic eruption at the consultation.

6 patients were treated with an anticoagulant medication (three with aspirin (Kardegic 75 ®), one with clopidrogel (Plavix 75 ®), and two with Apixaban (Eliquis ®). The investigations of biologic markers were conducted by the same laboratory and included platelet count (by impedance) and D-dimer titer (D-Dimer HD500, ACL TOP werfen). The time elapsed between the last vaccine injection and the blood test ranged from 1 to 10 months (mean: 3.8 months). The reference for a positive D-dimer is fixed at 500 µg/L. However, it is universally recognized that the D-dimer normal value is variable and must be age-adjusted. To overcome this problem and improve the specificity of the test, we fixed an age-adjusted D-dimer cut-off (patient's age x 10 µg/L) as proposed by Douma et al.[2]. Moreover, to eliminate minor variations we have stratified the results in three classes: normal, mild augmentation (between 10 and 50 % augmentation) marked augmentation (over 50 %) augmentation.

RESULTS

12 out 17 patients underwent a minor surgical procedure under local anaesthesia 8 teeth extractions, 4 dermatologic surgeries) and no related complication was observed. The platelet count was ranging from 114 to 373 G/L (mean: 245 G/L). In two patients there was a low platelet count

under 140 G/L that did not provoke any complications. The D-dimer level ranged from 215 to 7500 µg/L (mean: 1490 µg/L). In our classification, 5 (29.4%) had a normal value, 5 (29.4) % had a mild augmentation, and 7 (41.2) % a marked augmentation.

Considering other values, one patient had an abnormal hemogram showing a leukocytosis (15G/L) affecting all white blood cells type that is currently under investigation. The patient who had the highest level of D-dimer one month after the last injection with Comirnaty had a previous COVID infection after the third dose and a control blood test three months after the last injection showed that the level of D-dimer had decreased to 916 µg/L.

DISCUSSION

Since the introduction of COVID-19 vaccines, only sporadic biological perturbances have been observed, mainly focused on coagulation, but this alert provoked in France the withdrawal of AstraZeneca and Janssen vaccines as frontline vaccines. However, all other vaccines remain recommended as a booster dose on the hypothesis of a declining immunity that is difficult to verify as the number of COVID-19 has dramatically decreased. For this reason, there is urgent necessity to re-evaluate the benefit-risk ratio of all available COVID-19 vaccines. Clinically, our real-world practice confirmed the overestimated COVID-19 vaccine effectiveness in initial reports and there is a strong signal that all COVID-19 vaccines trigger Zoster reactivation [3]. But, as it may have an incidence on our practice, we are more particularly focused on hemostasis parameters. Regarding the platelet count, we found only a mild decrease in two patients and the results can be considered as reassuring.

Among other parameters, D-dimer has received special attention because it has been shown in a recent study that is a valuable test for early detection of vaccine-induced thrombocytopenia and thrombosis (VITT) [4]. The results on D-dimer level in our study indicate a more pronounced rise in D-dimer levels in 4-shots COVID-19 vaccinated patients but the interpretation of these results remained conditioned by the same problems reported in our previous study [1]. First of all, D-dimer modification is not specific of a pathology [5]. As stated in our previous paper, the other main obstacle for developing a scientific discussion is the paucity of undisputable comparative studies on the subject. To our knowledge, we found only three relevant papers in the main medical database (PubMed, Google Scholar, Research Gate) allowing clinical comparisons [6, 7, 8]. However, the variable methodologies used in these studies raise unsolvable problems. Thus, the first one [6] is a case report and it is impossible to extrapolate a general conclusion from this case. It also difficult to draw a conclusions from the two others because of the different design, and also as they have diverging results [7, 8]. In the first study [7], the authors noticed a regular increase of D-dimer level after the first dose of AstraZeneca vaccine; however, the blood sample was collected 2-3 days after the vaccine shot and it is usual to have a mild inflammation after any vaccines that can lead to a transient D-dimer increase. The second study is more solid with a large population of 567 healthcare workers: however, the conclusions remain disputable because it was conducted on patients who received only two shots of vaccines while most of the population has now received three shots. Moreover, the fragility of these conclusions is highlighted by more recent data that have revealed that AstraZeneca is the vaccine formulation that gives more coagulation disorders, although none of all others COVID-19 vaccines are exempted of this problem. Thus, both studies emphasized the main problem with the current vaccine trials that is their lack of standardization. The determinant parameters that should be taken into consideration in the carrying of these studies are the type of vaccines, the number of doses and the timing of the evaluation. Another ethical problem is the independence of the researchers, but this problem can be solved easily by the declaration of any conflict of interest. For these reason, we believe that our small study deserves consideration as it is the only one available studying D-dimer levels in 4-shots COVID-19 vaccinated patients and it is relevant as it confirm our previous findings. However, our conclusions are debatable as our observation time is shorter than in our previous study. Our results must also be taken cautiously as most of our patients have comorbidities that can lead to confusing deductions [8]. Furthermore, our findings are troublesome but must be taken prudently as we have not noticed any unexpected problem as reported in a similar Danish study on routine D-dimer checking [9].

In conclusion, our pioneer study indicates a D-dimer rise that may be linked to a prolonged post-vaccinal inflammation; however it was reassuring to observe no relationship with any adverse outcome of surgery in patient with abnormal D-dimer values. Nethertheless, it is admitted that D-dimer level is useful as a predictive unfavorable outcome indicator and we agree with Fazio and Affuso [10] that it would be useful to undertake on a large scale an independent and well-designed study to follow the possible inflammatory effects of the COVID-19 vaccines and to place patients with abnormal results under careful observation.

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