

STUDY OF HYPERSENSITIVITY REACTIONS TO COVID-19 VACCINES

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RESUMEN

COVID -19 vaccines have been mild to moderate and of short duration in our health area. These include fever, tiredness, headache, muscle pain, chills, nausea, diarrhea, and pain at the injection site. The chance of any of these side effects depending on each COVID-19 vaccine, and vaccines are constantly monitored for unusual side effects. In this study we assess the tests performed in the Allergy Unit of our Hospital, on patients referred to rule out a hypersensitivity reaction that could jeopardize the next dose. Of the 511 patients scheduled for vaccination at the Río Hortega University Hospital (HURH) in the West Valladolid Health Area, only 459 (89.8%) attended. Of which, 93.7% (CI 91.3-96) did not suffer/report hypersensitivity reactions. And of those that did, only 0.4% (95% CI: 0.05-1.56) were serious, and none were fatal. We conclude that there are no major limitations to the administration of the COVID vaccine in the general population or in the allergic or atopic population. It is to be expected, after the administration of the vaccine, the appearance of pain at the puncture site of high intensity. And there may be an association between the presence of fever and the positive result of immunoallergic tests.

INTRODUCTION

At the beginning of this year 2022, 92 million doses have been administered in Spain and 38 million people have received the complete vaccine, 80.3% of the population.

The chance of any of these side effects depending on each COVID-19 vaccine. More serious or long-lasting side effects are possible, but are extremely rare. Vaccines are constantly monitored for unusual side effects.

Of the 511 patients scheduled for vaccination at the Río Hortega University Hospital (HURH) in the West Valladolid Health Area (ASVAO), only 459 (89.8%) attended. Of which, 93.7% (CI 91.3-96) did not suffer/report hypersensitivity reactions.

In the present study we assess the tests performed in our Allergy Unit on referred patients to rule out a hypersensitivity reaction that could jeopardize the next dose.

Cases of adverse reactions to coronavirus vaccines in Spain have been very low and in no case serious. Until November 14, 2021, 71,746,002 doses of vaccines against COVID-19 have been administered in Spain,

with 50,824 notifications of adverse events having been registered, understanding as such any adverse event that requires or prolongs hospitalization, gives rise to significant or persistent disability or congenital malformation, life-threatening or fatal, as well as any other condition considered clinically significant.

71% of the doses administered corresponded to Pfizer Comirnaty, 13% to Vaxzevria (formerly COVID-19 Vaccine AstraZeneca), 13% to Spikevax (formerly COVID-19 Vaccine Moderna), and 3% to COVID-19 Vaccine Janssen (Source: *Vaccination Registry, Ministry of Health*).

The adverse reactions reported are mild, of short duration and not everyone gets them.

The Centers for Disease Control and Prevention (CDC) and the *Emergency Use Authorization* (EUA) have considered a severe allergic or anaphylactic reaction to the first dose of the vaccine or any component of the vaccine to be a contraindication to its use. However, in Spain the vaccine is not contraindicated in people with food allergies, medicines, animals, insects, environmental allergens or latex. There is only one case

in which it is contraindicated, and that is a specific allergy to polyethylene glycol (PEG).

This is because, despite the fact that the immunogenic mechanisms of anaphylaxis are still unknown, there seems to be an implication of this molecule in the process, which is present in the vaccines synthesized with mRNA, to date Pfizer-BioNTech and Moderna.

This genetically modified mRNA provides the cells of the organism receiving the vaccine with the information necessary to synthesize a substance, protein S, present on the lipid surface of the COVID19 virus. This allows the body to present said protein to the cells of the immune system, simulating a virus infection, stimulating them to generate antibodies, so that it is prepared to fight a possible future virus infection.

The viral vector of the vaccine contains Polysorbate, which is structurally related to PEG, and which also appears to have been implicated in anaphylactic-type reactions. Although it is true that in the majority of registered cases there was a history of allergy to a wide variety of other allergens.

The cases of anaphylaxis after the administration of these vaccines reported to date are estimated at around 5 cases per million inhabitants 0.005% (*Reports of Anaphylaxis despues de Receipt of mRNA COVID-19 Vaccines in the US- December 14, 2020-January 18, 2021.*)

In the Allergy department of our Río Hortega University Hospital, we have tested excipients similar to those contained in the Pfizer vaccine, particularly Moviprep (normally used in bowel preparation prior to colonoscopy), which contains PEG. In this line, the Moderna vaccine contains Trometamol, a component common to ketorolac (an NSAID) in ampoules, for which the hypothesis of possible allergological associations has also been raised and, therefore, hypersensitive patients to this group of analgesics have been warned.

PEG is used in molecules of different weights in many products. Recent studies suggest that patients allergic to this substance may react to nanoparticles PEGylated, but not against PEG alone. (*In vivo and in vitro testing with PEGylated nanoparticles. Kelso JM. SW. J Allergy clinic Immunol. 2021; 148(3): 902. Epub 2021 June 26.*)

The aim of this study is to evaluate the possible adverse effects of the vaccinated population in our health area. So far, reactions to this vaccination are lower than those observed with penicillins (0.002%). Analyzing all the variables involved can make it possible to obtain objective and truthful information about the safety of vaccines and, together with the data provided by the Ministry of Health, select the optimal type of vaccine for patients belonging to risk groups.

Our study is in accordance with the RIS3 objectives of the proponent and/or with the State Strategy for Science, Technology and Innovation.

JUSTIFICATION

Our study aims to evaluate hypersensitivity reactions to the COVID vaccine, specifically to the first dose of the one created by the Pfizer Comirnaty Laboratory.

This is interesting from two points of view: the medical (allergological in our case), and from a social perspective.

On the one hand, the evaluation of the impact of vaccination on the population reveals the efficiency and richness of the means available to it, while at the same time allowing conclusions to be drawn about the changes to be made in the face of a similar situation in a future scenario, that is, the appearance of a new disease that requires a vaccination process similar to that experienced with the SARS-CoV-19 virus.

On the other hand, objective indicators of the safety of vaccines are needed, which allow guidelines to be established on which to act in cases of patients allergic to certain components of the vaccine, or to other substances. That is, in short, to evaluate the interaction between factors related to postvaccinal reactions.

Why the COVID vaccine?

First, the administration of the vaccine to a large population in a short period of time makes the detection of adverse reactions especially important in terms of safety and efficacy. This makes it necessary to obtain objective and sensitive data that allow comparisons to be made at any time and place, such as those derived from our study.

At the same time, the novelty of the matter is relevant both for its bibliometric impact as well as its care, clinical and/or technological development impact, and makes it especially susceptible to being disseminated to a society that is sensitized and concerned about the possible secondary effects of the administration of these vaccines.

Why hypersensitivity reactions ?

To begin with, the molecular study from the immunoallergic point of view allows us to analyze its implication in the different clinical processes. The study of patients vaccinated in our Health Area complements the data collected by the Pharmacovigilance Service and the Vaccination Service of the Ministry of Health, which contributes to the correct selection of vaccines that can be administered to patients belonging to certain risk groups.

In this regard, cases of allergic history, reactions to NSAIDs or intolerance to contrast agents or polyethylene glycol are of special interest, from the epidemiological

and allergological point of view, given the potential allergenic risk suffered by these patients.

LIMITATIONS

The sample size, by including only patients vaccinated in the HURH, has been able to compromise the representativeness of the sample, so that the results obtained may be far from the characteristics of the reference population and may correspond less with those collected by the Valladolid Pharmacovigilance Service.

This may also have been accentuated by losses in case processing. In the same way, the aforementioned has been able to compromise the statistical significance of the variables included in the univariate and multivariate analysis.

One possible cause of the small sample size is the absence of notification by the patients under study due to their mildness, or the inconvenience derived from mobilization to the hospital to report their symptoms.

The pandemic situation has overwhelmed the capacities of the HURH registry centers and the Pharmacovigilance centers, so it has not been possible to obtain the numerical record of administered doses of the Pfizer vaccine in the HURH, nor the number of notifications of adverse reaction to the Pharmacovigilance service differentiated by areas in the province of Valladolid.

MATERIAL AND METHODS

- Study design. This research project is configured as a descriptive observational cross-sectional study.

It began in January 2021 and ended in October of the same year, prior to the arrival of the omicron variant.

- Study subjects. The study population comes from the database of health workers vaccinated at the HURH, with a size of 459 people (511 called but 52 did not attend).

From all of them, a sample of 29 patients diagnosed with hypersensitivity to the vaccine was obtained, without differentiation by sex or age.

The control group, concurrent, is made up of 29 healthy people, who have never attended an allergy clinic, randomly chosen by the HURH Allergy Unit.

- Variables. The main variables studied were the following:

- Prick Test result
- Presence of a history of immunoallergic type, considering as such anaphylactic reaction to the triple viral vaccine and allergy to contrast agents.
- Presence or absence of the following symptoms, along with their degree of intensity (from 1 to 5 on a Likert scale): Lymphadenopathy, insomnia, headache, nausea, abdominal pain, diarrhea, arthralgia, myalgia, puncture pain, inflammation, puncture erythema, puncture pruritus, brachialgia, functional limitation, hand paresthesia, asthenia,

dysthermia, malaise, low-grade fever, fever, facial paralysis, nightmares, hypersensitivity, anaphylaxis.

- Presence of other symptoms

- Data Collect. In the data collection, the Jimena® IV and Clinical Report Manager computer programs were used to access the clinical history and collect the pertinent information, which was organized in an anonymized database. The study was approved by the corresponding Ethics Committee of the West Valladolid Health Area.

For the calculation of the sample size, an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast were accepted. A rate of loss to follow-up of 20% was estimated.

First, an exhaustive bibliographic search was carried out (*Clinical queries, SUM Search, Grade, Cochrane Library*) on the relevant information published at the beginning of the study.

The criteria of the CONSORT regulations of February 2009 and of QUALITY 2011 of the Rio Hortega University Hospital were applied, always prevailing the safety and comfort of the patients under study, attending to the Declaration of Helsinki and UNESCO, as well as offering verbal information of the process. and a written informed consent.

Initially, patients with hypersensitivity to the vaccine were detected, in order to proceed to an allergological diagnosis, using advanced techniques from the Allergology Service. Understanding as hypersensitivity the classification of Gells and Coombs, which establishes 4 types.

Hypersensitivity is understood as any exaggerated body response to foreign antigens that are harmless to the body. The first contact with Ag does not generate any allergic reaction, but it does generate memory cells.

Then, after giving their informed consent, the patients underwent a clinical-epidemiological survey that included: data on the vaccine administered (Pfizer-Comirnaty), on past illness (date of onset of symptoms, date of positive PDIA, if any), and discharge date). As well as a list of side effects after vaccination, to mark indicating intensity on a Likert scale, time elapsed from the administration of the vaccine to the appearance of adverse effects and from these to their complete remission.

Exclusively "in vivo" tests were carried out with Covid vaccines and excipients, following the standards of the Spanish Society of Allergy and Clinical Immunology (SEAIC).

For the "in vivo" tests, the following products were used:

1. VACCINES (excess of the day, 6 hours of activity. Immediate reading. Prick 1:1 and intradermal 1:100 and 1:10)
2. PEG (Polyethylene glycol), prepared in the Pharmacy Service: Two products were used: MOVICOL 3,350 dissolved in 250 ml at 1:2 and CASENLAX 4000 dissolved in 250 ml at 1:2
3. Intradermal tests: only in patients without anaphylaxis or without previous comorbidities, with IV route.
4. TWEEN 80 in prock and ID: 0.004 mg/ml in water (SIGMA)
5. TROMETAMOL (contained in MODERNA vaccines) in water (SIGMA). Prick 1:1 and ID (1:1000, 1:100, 1/10)
6. Skin tests with environmental and food allergens: They were performed with the conventional prick technique for the case of marketed allergens. The prick tests were carried out in accordance with the standards of the European Academy of Allergy and Clinical Immunology (EAACI). Thus, after depositing a drop of each allergen to be tested in the volar area of the forearm, a minimal puncture was made, which should not reach the dermis, through the drop with a lancet. The excess extract was then removed and after a waiting time of 30 minutes, the result was read, considering positive that test that produced a wheal whose largest diameter was equal to or greater than 3 mm. Each allergen was tested in duplicate and the results were recorded on a data collection sheet for later digitization.

The controls were administered physiological serum and Histamine to evaluate their result in the Prick test, which was negative in all cases.

- Analysis of data. For the statistical analysis and the creation of the database, the statistical program IBM

SPSS Statistics was used. The degree of association between the qualitative variables (result of the Prick test and the symptoms) was determined through the Pearson test, with the Chi-square contrast statistic; and the association between the degree of intensity and the result of the Prick was determined by means of the Student's t-test. A value of $p < 0.05$ was considered statistically significant. Throughout the study, missing data were statistically treated as unknown values. The qualitative variables have been described with the mean (SD) or median (interquartile range p25-p75).

- Stages of development. The work was carried out at the Río Hortega University Hospital. Allergy Unit, Research Unit. Río Hortega University Hospital in Valladolid and in the Preventive Medicine Unit. Once the study was explained to the patient and the informed consent signed, the following protocol was carried out:

1. Anamnesis and diagnosis of allergy to COVID vaccine
2. Clinical-epidemiological questionnaire
3. Random selection of patients and review of inclusion criteria. Skin prick tests with vaccine extracts and aeroallergens.
4. Statistical analysis of the data (SPSS.15)
5. Final evaluation

RESULTS

The absolute and relative frequency of hypersensitivity reactions reported to the HURH allergology service is shown in **Figure 1**. Of the 511 patients scheduled for vaccination, only 459 (89.8%) attended. Of which, 93.7% (95% CI: 91.3-96) did not suffer or report hypersensitivity reactions. Of the remaining 6.3%, 0.4% (95% CI: 0.05-1.56) were severe reactions, 5.9% (95% CI: 3.6-8.1) were mild or moderate, and there were none fatal.

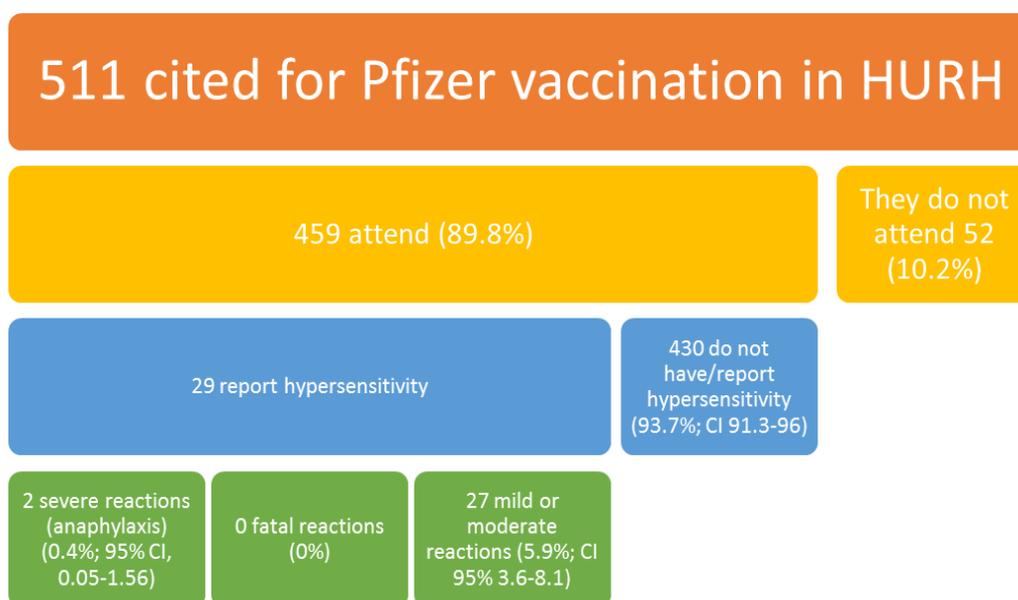


Figure 1: Absolute and relative frequency of reported hypersensitivity reactions.

The absolute and relative frequency of hypersensitivity reactions notified to the Pharmacovigilance service of the

province of Valladolid is shown in **Figure 2**.

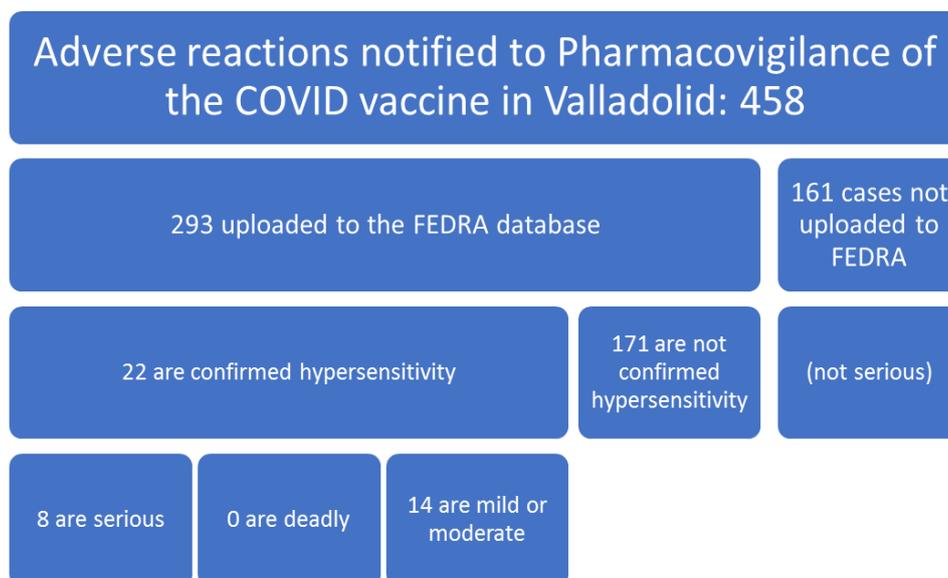


Figure 2: Absolute and relative frequency of hypersensitivity reactions notified to the Pharmacovigilance Service.

The difference in patients detected with hypersensitivity between the results of our study and those obtained by the Pharmacovigilance Service, with a degree of statistical significance $p=0.023$, is shown in **Table 1**.

In our study, 36.4% of all reported hypersensitivity reactions were serious, compared to 6.9% of those reported by the Valladolid Pharmacovigilance Service.

63.6% of the total reactions were mild or moderate in our study, as opposed to 93.1% with respect to the total notifications from the Pharmacovigilance service.

No anaphylaxis reaction was reported in any case.

Table 1: Difference in data on hypersensitivity notifications collected by the HURH and by Pharmacovigilance.

	OUR STUDIO <i>Degree of significance</i> $P=0.023$	PHARMACOVIGILANCE <i>Degree of significance</i> $P=0.023$
Serious reactions (anaphylaxis)	36.4%	6.9%
Deadly reactions	0	0
Mild or moderate reactions	63.6%	93.1%

The relationship between the intensity of each symptom and the percentage of patients who suffered from it with respect to the sample are shown in **Table 2**.

The most intense symptoms (Grade 5) were general malaise and anaphylaxis.

Most of the symptoms were intensity 4.

The symptom that appeared most often was pain at the puncture site, followed by nausea.

The least frequent symptom is paresthesia of the hand, of high intensity (grade 4), discarding diarrhea as an adverse reaction derived from the vaccine.

Table 2: Relationship between intensity of each symptom and percentage of patients who suffered from it.

SYMPTOM	No. (%)	INTENSITY
lymphadenopathy	6 (20.7%)	4 (3.7 ± 4.2)
Insomnia	7 (24.2%)	4 (4 ± 5)
headache	9 (31%)	4 (4 ± 4.5)
Sickness	12 (41.4%)	4 (4±5)
abdominal pain	10 (34.5%)	4 (4±4)
Diarrhea	0	0

Arthralgia	8 (27.6%)	4 (3.24±5)
Myalgia	9 (31%)	4 (4±5)
puncture pain	13 (44.8%)	4 (3.5±4)
Inflammation	8 (27.6%)	4 (3.25±5)
puncture erythema	8 (27.6%)	4 (2.5±5)
puncture pruritus	5 (17.2%)	3 (2.5±4.5)
brachialgia	6 (20.7%)	4 (3.75±4)
functional limitation	5 (17.2%)	4 (3±4)
Paresthesia hand	1 (3.4%)	4 (4±4)
Asthenia	5 (17.2%)	3 (3±5)
dysthermia	6 (20.7%)	4 (3.5±5)
General discomfort	9 (31%)	5 (4±5)
low-grade fever	7 (24.1%)	4 (3±5)
Fever	4 (13.8%)	3 (2±4.75)
Facial paralysis	2 (6.9%)	2 (2±2)
Nightmares	2 (6.9%)	2.5 (2±3)
hypersensitivity	5 (17.2%)	4 (2.5±4.5)
Anaphylaxis	2 (6.9%)	5 (5±5)

Other symptoms that occurred, not included in the epidemiological survey, but considered relevant due to their possible long-term significance, were:

- AHT 222/116 mmHg and non-pruritic erythema in the submental region and neckline
- Lip edema, dysphagia, macroglossia and hypertension 150/130 mHg.
- Shoulder epidermolysis.
- Hemi -right paresthesia and cramps.
- Herpes Zoster
- Micropapular lesions predominantly on the forehead and scalp.
- Odynophagia
- Prurigo.
- Urticarial reaction with respiratory compromise.
- Rhinitis

- Mild naso-ocular symptoms.

The relationship between the presence or absence of symptoms and the result of the Prick test is shown in **Table 3**.

The symptoms were statistically significant: dysthermia, low-grade fever and fever. Of these, low-grade fever was more frequent in patients with a negative Prick test, while fever was more frequent in patients with a positive Prick result. Dysthermia presented the same frequency in both cases A tendency towards the presentation of general malaise was revealed, especially in patients with negative Prick.

Table 3: Relationship between the presence or absence of symptoms and the result of the Prick test.

	Negative Prick	Positive Prick	Significance
Lymphadenopathy	5 (20%)	1 (25%)	1
Insomnia	2 (20%)	2 (50%)	0.238
Headache	7 (28%)	2 (50%)	0.568
Sickness	9 (36%)	3 (75%)	0.279
Abdominal pain	8 (32%)	2 (50%)	0.592
Diarrhea			
Arthralgia	6 (24%)	2 (50%)	0.3
Myalgia	6 (24%)	3 (75%)	0.076
puncture pain	11 (44%)	2 (50%)	1
Inflammation	6 (24%)	2 (50%)	0.3
Puncture erythema	6 (24%)	2 (50%)	0.3
Puncture pruritus	4 (16%)	1 (25%)	0.553
Brachialgia	4 (16%)	2 (50%)	0.18
Functional limitation	4 (16%)	1 (25%)	0.553
Paresthesia hand	0	1 (25%)	0.138
Asthenia	4 (16%)	1 (25%)	0.553
Dysthermia	3 (12%)	3 (75%)	0.02
General discomfort	6 (24%)	3 (75%)	0.076
low-grade fever	4 (16%)	3 (75%)	0.034
Fever	1 (4%)	3 (75%)	0.004

Facial paralysis	2 (8%)	0	1
Nightmares	1 (4%)	1 (25%)	0.261
hypersensitivity	4 (16%)	1 (25%)	0.553
Anaphylaxis	2 (8%)	0	1

The relationship between the intensity of the symptoms and the result of the Prick test is shown in **Table 4**

In general, a greater intensity of symptoms was observed in Prick -positive patients, with the exception of insomnia, nausea, and lymphadenopathy.

Table 4: Relationship between symptom intensity and Prick test result (Mean± SD.)

	Negative Prick	Positive Prick
Lymphadenopathy	4.2 ± 4.4	3 ± 4.4
Insomnia	4.2 ± 0.8	3 ± 0
headache	4.14 ± 0.7	4 ± 0
Sickness	4.11 ± 0.9	3.67 ± 1.5
Abdominal pain	4 ± 0	4 ± 1.4
Diarrhea	0	0
Arthralgia	4 ± 1	4 ± 1.4
Myalgia	4.33 ± 0.51	4.67 ± 0.57
puncture pain	3.82 ± 0.6	4 ± 0
Inflammation	4 ± 1.2	4 ± 0
Puncture erythema	3.83 ± 1.4	4 ± 0
Puncture pruritus	3 ± 0.8	5 ± 0
Brachialgia	3.75 ± 0.5	4 ± 0
Functional limitation	3.5 ± 1	4 ± 0
Paresthesia hand	0	4 ± 0
Asthenia	4 ± 1.1	3 ± 0
Dysthermia	3.33 ± 1.1	4.67 ± 0.6
General discomfort	4.33 ± 0.81	4.67 ± 0.6
Low-grade fever	3.25 ± 0.5	4.33 ± 0.6
Fever	2 ± 0	3.67 ± 1.5
Facial paralysis	2 ± 0	0
Nightmares	2 ± 0	3 ± 0
hypersensitivity	3.25 ± 0.97	5 ± 0
Anaphylaxis	5 ± 0	0

6. DISCUSSION

In our study, compared with the data collected by the Valladolid Pharmacovigilance Service, we can see a greater number of severe reactions, together with a lower number of mild or moderate reactions, possibly derived from our smaller sample size, but it is worth noting the value null of death derived from the vaccine in neither of the two cases.

limitations regarding the collection of information and the diagnosis of cases take on great relevance, highlighting the deficient capacity of the Pharmacovigilance system to face the demands derived from the pandemic.

It could also suggest a lack of information or ease on the part of patients to notify this type of reaction, not only in terms of those of the COVID vaccine, but all in general. However, the absence of notification is in favor of the mildness of the symptoms, since it is assumed that they did not require hospital care.

The symptom that occurred most frequently was pain at the puncture point, followed by nausea, with an intensity of level 4 out of 5 in both cases. Perhaps it would be advisable to consider preventive treatment of this symptom with metoclopramide or another similar drug, in order to increase patient comfort and adherence to vaccine administration.

The symptoms detected not included in the epidemiological survey are of special relevance due to their possible long-term repercussions, such as Herpes Zoster or hemiparesis, however we still cannot relate them to any specific patient profile or announce measures for their prevention.

On the other hand, regarding the relationship between the results of the Prick test and symptomatology, we obtained 3 statistically significant results, which were fever, dysthermia and low-grade fever. Found more frequently in patients with a negative test result. For this reason, it is conceivable that there is no relationship between these symptoms and the components of the

vaccine tested, and that the administration of Paracetamol concomitantly with the vaccine is especially

recommended to alleviate this effect, as recommended by international scientific societies.



Image 1: Herpes Zoster reaction.

Phase 1/2 study: Transient local and systemic reactions with AstraZeneca Covid-19 vaccine were slightly

decreased with paracetamol and occurred less frequently after the second dose.

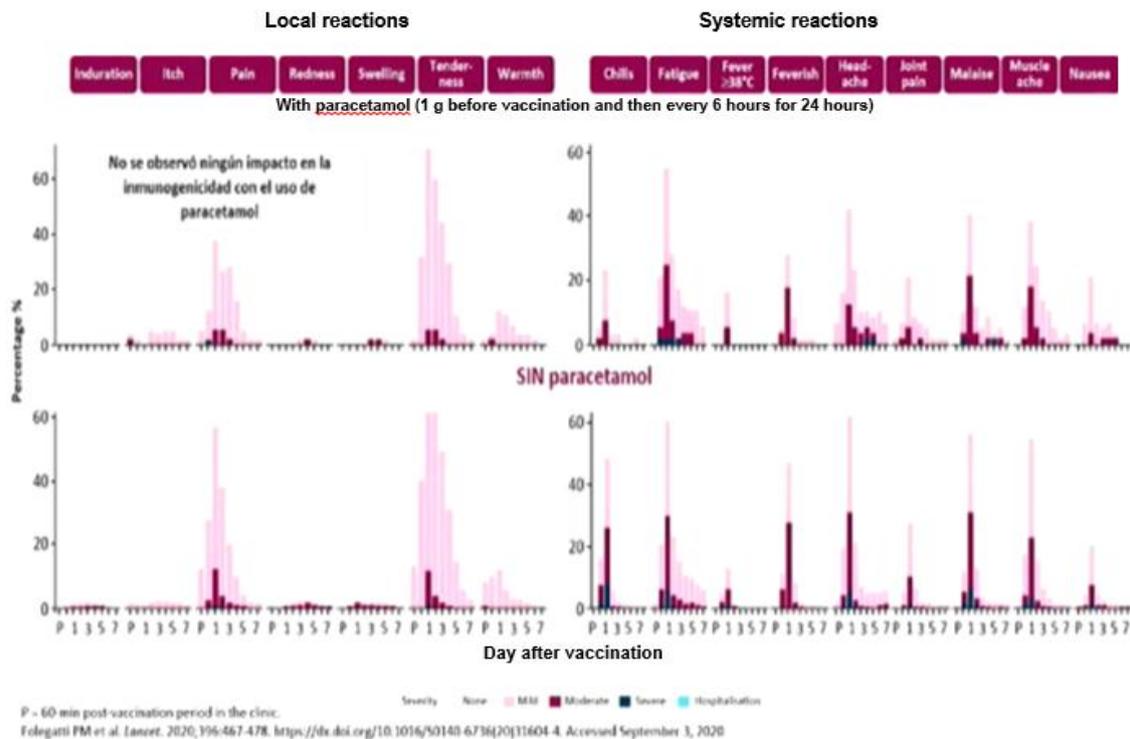


Figure 2: Incidence of transient reactions with AstraZeneca COVID vaccine with and without concomitant administration of paracetamol.

Likewise, a tendency towards general malaise, myalgias and paresthesias in the hand has been revealed, in the same way in patients with a positive and negative Prick result, so in this case there could be an association with PEG, Polysorbate, Trometalol, etc... However, this

information is consistent with post-vaccinal reactions typical of any other microorganism, which is a source of knowledge and peace of mind for patients.

The correlation between the frequency and percentage of symptoms and the time elapsed from their administration and until their appearance was also studied, but no results of interest were obtained. It should be noted that the most frequent minimum time of appearance was 12 hours, and in terms of disappearance, in some cases,

dermatological lesions (shoulder epidermolysis and micropapular lesions predominantly on the forehead and scalp) persisted at the end of the study. It is therefore possible that, despite the safety of the vaccine, irreversible reactions may occur in some cases.



Figure 2: Dermatological lesion at the puncture site.

The association with other history of hypersensitivity was evaluated, specifically allergy to radiological contrasts and anaphylaxis to the triple viral vaccine, finding no conclusions of interest. However, we cannot rule out the association with a history of atopy.

7. CONCLUSIONS

- 93.7% (95% CI: 91.3-96) of the patients under study had no hypersensitivity reactions.
- Of those that did, only 0.4% (95% CI: 0.05-1.56) were serious, and none were fatal.
- The initial hypothesis obtained from the information provided by the Ministry of Health is confirmed, which stated that fatal allergic reactions are non-existent, and serious ones are infrequent, being mostly mild or moderate, of the low-grade type and fundamentally general malaise.
- We can conclude, therefore, that there are no major limitations to the administration of the COVID vaccine in the general population or in the allergic or atopic population.
- It is to be expected, after the administration of the vaccine, the appearance of pain at the puncture site of high intensity.
- There may be an association between the presence of fever and the positive result of immunoallergic tests.

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