ISSN: 2577-2996

PROGRESS IN MEDICAL SCIENCES, 2022
VOL 6, NO. 6, PAGE 1 – 4
DOI: doi.org/10.47363/PMS/2022(6)180

RESEARCH ARTICLE

Open Access

Anti SARS-Cov-2 Vaccine in CRPS Patients

Sharon Halperin[1]*, Andrea Book[2], Moran Shextman[2], Israel Dudkiewicz[2,3] and Oren Barzel[2,3,4]

[1]Early Phase Clinical Trials Unit, Sheba Medical Center, Israel

[2]Orthopedics Rehabilitation Department, Sheba Medical Center, Israel

[3]Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel

[4]Ono Academic College, Kiryat Ono, Israel

ABSTRACT

Complex regional pain syndrome (CRPS) is a chronic pain syndrome defined by the presence of clinical features such as allodynia, hyperalgesia, sudomotor and vasomotor abnormalities. The pathophysiology of CRPS is not yet fully understood and is likely to involve pain dysregulation in the sympathetic and central nervous systems with genetic, inflammatory and psychological contributions. Data on the safety of SARS-CoV-2 vaccines in CRPS patients is sparse. We conducted a retrospective study on CRPS patients vaccinated with the BNT162b2 vaccine. The aim was to evaluate the willingness of CRPS patients to get vaccinated, the frequency and the severity of adverse events and whether the vaccine affected their chronic pain. The study included patients diagnosed with CRPS regularly visiting our CRPS outpatient clinic. The analysis included 34 patients (55% males, median age 42, 67% of the patients have CRPS of the upper limbs, 26 % have CRPS of the lower limbs and 7% in both upper and lower limbs). Twenty-seven patients received only one dose of the vaccine and 26 patients received two doses. For most patients (88%), the adverse events were well tolerated and did not have any effect on their CRPS pain. In conclusion, although this is a small patient cohort, the BNT162b2 was well accepted and tolerable among our CRPS patients.

Perspective: This study shows the adverse events profile of the anti SARS-Cov-2 BNT162b2 vaccine in CRPS patients. The two doses were well tolerated among our CRPS patients. This study may help physicians recommend the vaccine to their CRPS patients.

ARTICLE HISTORY

Received December 01, 2022
Accepted December 05, 2022
Published December 15, 2022

KEYWORDS: CRPS, Complex Regional Pain Syndrome, BNT162b2, Vaccine, COVID-19

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Introduction

Complex regional pain syndrome (CRPS) is a chronic pain syndrome defined by the presence of clinical features such as allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic changes [1]. The pathophysiology of CRPS is not yet clarified and is likely to involve pain dysregulation in the sympathetic and central nervous systems with genetic, inflammatory and psychological contributions [1]. CRPS can be divided into two subtypes, CRPS type I, also known as reflex sympathetic dystrophy, with the absence of major nerve injury, and CRPS type II, also known as causalgia with the presence of nerve injury [2]. Although the etiology of CRPS is still largely unknown, increased pro-inflammatory state has been shown in both acute and chronic CRPS [3].

Recent evidence supports a role of immune activation dysregulation and subsequent inflammation with increased levels of proinflammatory cytokines, higher prevalence of various autoantibodies and increased activity of T lymphocytes [4]. Reactogenicity represents the physical manifestation of the inflammatory response to vaccination and can include local reactions such as injection site pain and redness, and systemic symptoms such as fever and chills, myalgia, headaches and fatigue. Vaccines induce an immune response that includes the release of inflammatory mediators such as proinflammatory cytokines and chemokines and activation and recruitment of immune cells [5]. There is currently, no published information about adverse reactions after immunization in CRPS patients, both from the injection itself or the reactogenicity of the vaccine, and whether vaccinations cause worsening of the preexisting chronic pain. There is some evidence of immunization causing clinical CRPS symptoms, but not enough to show causal correlation between the two [6-8]. As far as we know, no data was collected about adverse events and general worsening of chronic pain in CRPS patients after vaccinations in general, and after COVID-19 vaccines in particular.

Contact Sharon Halperin ✉ Sharon.Halparin@sheba.health.gov.il Early Phase Clinical Trials Unit, Laboratory Wing, Sheba Medical Center, Israel.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting coronavirus disease (COVID-19) was declared a pandemic by the World Health Organization on March 11 2020 [9]. In December 2020, the mRNA COVID-19 vaccine was approved by the Israeli government, and by Dec. 20th, 2020, the Israeli Ministry of Health launched a nationwide Pfizer BNT162b2 vaccination campaign. Two doses of the BNT162b2 vaccine (Pfizer, New York, USA and BioNTech, Mainz, Germany) were administered at the standard recommended two doses, 21 days apart. Although there is no contraindication for CRPS patients to get vaccinated, the large phase 3 trials on the BNT162b2 vaccine did not include CRPS patients and caused uncertainty in both CRPS patients and the treating physicians [10]. Here, we describe the adverse effects of BNT162b2 vaccination on CRPS patients. Our aim was to evaluate the willingness of CRPS patients to get vaccinated, the frequency and the severity of their adverse events profile, and whether the reactogenicity of the vaccine and proinflammatory state affected the pain profile of these patients.

Methods

Study Design and Participants

From January 2021, physicians in Israel recommended the Israeli population to get vaccinated with two BNT162b2 vaccine doses with the recommended 21 days wait between doses. Patients undergoing active follow-up at the rehabilitation center's outpatient CRPS clinic at Sheba Medical Center were screened for the confirmed diagnosis of CRPS. All patients were offered to participate in this study and to answer a specific questionnaire with the study staff. Informed consent was obtained from all participants. The protocol and informed consent were approved by our institutional review board.

Clinical Data Extraction

The specific questionnaire included whether the patient got vaccinated with the first and second dose, reasons why a patient did not get vaccinated, known adverse events of the vaccine and any other adverse events, duration of adverse events, effect of the vaccine on the chronic CRPS pain and whether they needed to increase pain medications.

Clinical data was retrieved from the electronic medical records and included, age, gender, CRPS type, CRPS symptoms localization, whether they were infected with SARS-CoV-2, comorbidities and concurrent medications.

Safety

Adverse events (AEs) were obtained using a specific questionnaire, which included local reactions such as pain, redness and swelling at the injection site, systemic reactions such as fever and chills, fatigue, headache, myalgia, nausea and vomiting and any general worsening of the existing chronic pain.

Results

Patient Characteristics

Patient characteristics are shown in Table 1. Thirty-four patients enrolled in our study. The median age was 42+10.6 years (range 22-73 years). Nineteen (55.88%) were males, 31 (91.17) had Type I CRPS, 23 (67.64%) with pain localized in the lower limbs. Twenty-three (67.64%) had comorbidities including PTSD (8, 23.52%), fibromyalgia (3, 8.82%) and others. All patients were taking pain and other concurrent medications, including cannabis (23, 67.64%), analgesics (22, 64.7%), neuropathic pain medication (19, 55.88%), psychiatric medication (16, 47%) insomnia medication (9, 26.47%) and other medications (17, 50%).

Twenty-seven (79.41%) patients received the first dose of the vaccine and 26 (76.47%) also received the second dose. The reason for one patient not receiving the second dose was a prior diagnosis of COVID-19. Seven patients did not want to receive the vaccine and the reasons were disbelief in vaccines, distrust in the specific vaccine, fear of side effects, fear of chronic pain worsening and medical contraindications.

Table 1: Demographic and Clinical Characteristics of CRPS Patients

		CRPS patients N=34
Gender N (%)		
M	19	(55.88)
F	15	(44.11)
Age mean±SD	42	±10.6
CRPS Type N (%)		
I	31	(91.17)
II	3	(8.82)
CRPS pain localization N (%)		
Lower limb	23	(67.64)
Upper limb	9	(26.47)
Lower and upper limb	2	(5.88)
Comorbidities - any N (%)	23	(67.64)
PTSD	8	(23.52)
Fibromyalgia	3	(8.82)
Deep vein thrombosis	3	(8.82)
Osteoporosis	2	(6.06)
Other	20	(45.45)
Concurrent medications ANY N (%)	34	(100)
Cannabis	23	(67.64)
Analgesic Drugs	22	(64.7)
Neuropathic Pain Medications	19	(55.88)
Psychiatric Medication	16	(47)
Insomnia Medication	9	(26.47)
Anti-inflammatory	4	(11.76)
Anti-coagulation	3	(8.82)
Other	17	(50)

Safety Profile of the BNT162b2 Vaccine: Adverse Events

Vaccine-related serious adverse events were not observed among the study population. Fifty one percent (14) of the patients reported at least one AE after the first dose of the vaccine and 42% (11) after the second dose (Table 2), with mild-to-moderate reactions. Of those who were vaccinated, 5 (18.51%) were at the age of 55 and above and 22 (81.48%) were below 55 years old. The younger group reported more local reactions with 12 (54.55%) reporting local pain, redness or swelling at the injection site. None reported local reactions in the older age group after the first dose. After the second dose, eight (36.36%) patients from the younger age group and one (25%) patient from the older age group reported local reactions.

Systemic reaction were less common, with fatigue being the most common after the first dose in both the younger and older groups (31.82% and 20% respectively), and after the second dose in the younger group (13.63%), with none in the older group. All AEs subsided within 24-48 hours with no need for additional pain or other medications.

Table 2: Adverse Events Among CRPS Patients

	CRPS patients age>55		CRPS patients age<55	
Patient received 1st vaccine	5		22	
Any AE after 1st vaccine N (%)	2	(40)	12	(54.55)
Local pain, redness or swelling at injection site	0	(0)	12	(54.55)
Myalgia	1	(20)	2	(9.09)
Fever or chills	0	(0)	2	(9.09)
Headache	0	(0)	2	(9.09)
Nausea and vomiting	0	(0)	0	(0)
Fatigue	1	(20)	7	(31.82)
Worsening of chronic CRP pain	1	(2.94.)	2	(9.09)
Patient receives 2nd vaccine	4		22	
Any AE after 2nd vaccine	2	(50)	9	(40.91)
Local pain, redness or swelling at injection site	1	(25)	8	(36.36)
Myalgia	1	(25)	1	(4.55)
Fever or chills	1	(25)	1	(4.55)
Headache	2	(50)	1	(4.55)
Nausea and vomiting	2	(6.06)	1	(4.55)
Fatigue	1	(25)	3	(13.63)
Worsening of chronic CRP Spain	0	(0)	2	(9.09)

Safety Profile of the BNT162b2 Vaccine: Worsening of the Chronic CRPS Pain

Only three patients (one patient in the older group and two patients in the younger group 11.11%) reported worsening of the already existing chronic pain related to the CRPS after the first dose and two patients (7.5%, both in the younger group) after the second dose. None of the patients reported new severe acute or chronic pain at least six months after the second dose.

Discussion

There was an urgent need in finding a vaccine for the COVID-19 pandemic. All major clinical trials with the BNT162b2 vaccine did not include chronic pain patients such as CRPS patients and the uncertainty of vaccination in these patients grew over time. In this study, we found that the adverse events profile is similar and maybe even lower to what Polack FP et al. showed in Pfizer's phase 3 clinical trial on the general population [10]. Local reactions were more common than systemic reactions in the younger aged group (<55) than the older aged group (>55), in line with what was reported in the general population. Vaccinations, also called immunizations, can cause various immune responses. CRPS patients are thought to be in a constant proinflammatory state and immunization may amplify the already defective immune system and increase CRPS symptoms including pain. We showed that only three patients (11.11%) had mild to moderate worsening of their chronic CRPS pain after the first dose and only two patients (7.5%) had worsening pain after the second dose. This observation can be explained by the constant chronic pain masking any new low-level pain possibly caused by the vaccine. Another explanation can be the many pain medications taken by CRPS patients mask the possible local and systemic pain caused by the vaccination.

The major limitations of this study are the small number of patients enrolled in this study and the type of patients. Data was obtained from a small group of patients who regularly come to our CRPS outpatient clinic. These patients are generally more independent with day-to-day activities and in better control of their chronic pain. Response to vaccinations with other patient groups may differ. Thus far, approximately three million Israelis received a third booster vaccine six months after the second

dose. Patients in our study population who received the first two doses showed willingness to get the third booster dose and would not hesitate to receive it when available for them. Data on more CRPS patients should be obtained to assess the full adverse effects profile of the BNT162b2 on CRPS patients after the second and third dose.

In conclusion, the safety profile of the BNT162b vaccine in CRPS patients is similar to the general population and the rate of local and systemic AEs is lower. Worsening of the chronic CRPS pain was resolved with no intervention, and none of the patients reported any new chronic pain after six months from the second dose. In these times of the COVID-19 pandemic, where we observed that in some CRPS patients, the general condition worsened due to stress, and they were unable or afraid to get out of the house for clinic visits or treatments, the COVID-19 vaccine has been a safe and tolerable solution.

Acknowledgment: We gratefully acknowledge all of the CRPS outpatient clinic staff and Orthopedics rehabilitation department at the rehabilitation hospital, Sheba Medical Center.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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