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International Journal of Clinical Case Reports and Reviews

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Research Article

Treatment of Covid-19 Ambulatory Patients with A Medicinal Preparation of Echinacea Purpurea: The Ecco-2 Investigator-Initiated, Randomised, Double Blind, Controlled Trial

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Received Date: December 24, 2024 | **Accepted Date:** January 08, 2025 | **Published Date:** January 31, 2025

Citation: Marta J. Domingo, Azucena P. Zapico, Cristina R. Castro, Juan E. Cuello, Jesús R. Requena, et al., (2025), Treatment of Covid-19 Ambulatory Patients with A Medicinal Preparation of Echinacea Purpurea: The Ecco-2 Investigator-Initiated, Randomised, Double Blind, Controlled Trial, *International Journal of Clinical Case Reports and Reviews*, 22(5); **DOI:10.31579/2690-4861/651**

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Abstract:

Background: The COVID-19 pandemic has affected millions throughout the entire world, causing an unprecedented disruption of the daily lives of many more millions. While vaccines have proven to be a powerful prophylactic tool co contain the spread of the disease, treatment options are very limited. Echinacea phytotherapy is known to be efficacious in the treatment of mild respiratory viral infections, therefore we and others hypothesized that it might be helpful in the treatment of ambulatory COVID-19.

Purpose: To evaluate the clinical efficacy and safety of a medicinal preparation of cryo-milled root of Echinacea purpurea added to the standard-of-care (SOC) treatment in ambulatory COVID-19 patients with mild clinical symptoms, with a respiratory profile.

Methods: We designed and conducted a prospective, double-blind, multicentre, randomized, controlled clinical trial involving four hospitals in Spain, from July 2021 to June 2022. Participants were ambulatory adults with COVID-19 infection, assessed by a positive PCR or antigen test, with mild symptoms of a respiratory profile. Patients were given Echinacea Arkopharma, hard caplets containing 250 mg of Echinacea purpurea (L.) Moench, 1.5 g/day (2 caplets every 8 hours, i.e., 6 g/day, 7 days) added to standard care (vide infra). Participants were followed for 28 additional days. The primary outcome of effectiveness (OE) was OE1: number of days with fever (body temperature ≥ 37ºC at any moment of the day). The secondary outcomes were OE2: days with subjective dyspnea, OE3: days with unsaturation (≤ 96%), OE4: days with disease, OE5: percentage of hospitalizations, OE6: length of hospitalization (days), OE7: days of sick leave, OE8: percentage to visits to emergency room, OE9: percentage of admissions to intensive care units, OE10: percentage of deaths, OE11: subjective perception by the recruiting physician of the treatment usefulness to improve the evolution of the disease, OE12: subjective perception by the patient of the treatment usefulness to improve the evolution of the disease. The secondary outcomes of safety (OS) were OS1: incidence of respiratory adverse effects, OS2: incidence of palpitations (> 110x'), OS3: incidence of transaminase elevations (AST level ≥ 3x the normal range limit), OS4: incidence of headaches, OS5: incidence of digestive adverse effects, OS6: incidence of insomnia and nervousness. For all cases, OS1 to OS6, percentage of dropouts for that specific reason.

Results: The target recruitment number, 230, was not achieved. Rather, 99 eligible patients could be recruited (age 35.50 ± 11.9 years; 51.5 % female). They were randomised to SOC + treatment (n=50) and SOC + placebo group (n=49). There were no statistically significant differences between the treatment and placebo groups in the main variables studied, however, it should be noted that an important limitation of the study is the fact that we could not reach our recruitment target by far. Incidence of serious AEs was nil. Mild AE consisting of diarrhea were seen in 2 cases, and 1 effort- induced tachycardization, although there is no statistical evidence supporting that they were caused by the treatment.

Conclusion: Echinacea, added to the SOC treatment for mild COVID-19, was safe and well tolerated but had no major impact on clinical outcomes. Some effectiveness trends suggest that further studies with full recruitment are warranted to definitively assess its efficacy in moderately affected COVID-19 patients.

Key words: covid-19; echinacea purpurea; clinical trial

Introduction

The COVID-19 pandemic has affected millions throughout the entire world, causing an unprecedented disruption of the daily lives of many more millions. It has caused more than 6 million deaths so far, and many more million patients have been left with sequelae from the disease.[1] COVID-19, caused by the SARS-Cov-2 coronavirus, manifests itself as a respiratory infection, with or without an associated pneumonia, with a myriad of possible additional affections in many organs and systems. In this respect, SARS-CoV-2 can be considered a lymphotropic and neurotropic virus. The abnormal inflammation that ensues occasionally plays a key role in the subsequent pathology and has been related to "long COVID", a constellation of clinical signs and symptoms that persist for at least 8 weeks after disease inception.[2] Around 5%–10% of infected patients experience severe or life-threatening symptoms with high mortality.[3] COVID-19 spread very quickly throughout the World during 2020 and 2021. In 2022 its incidence started to diminish greatly, particularly in Europe and North America thanks to massive vaccination.[4] Echinácea purpurea is a plant original from North America that has been used in traditional herbal medicine for the treatment of injuries, skin and respiratory infections, and gastroenteritis among other ailments.[5] Echinacea preparations are widely used currently as coadjuvants for the prevention and treatment of common colds caused by different coronaviruses.[6-8] A number of recent studies have shown that when ingested, its active principles (alkamides, chicoric acid, quercetin, flavonoids such as rutin, nicotiflorin, glucoproteins and others) acted synergistically to stimulate the innate immune system.[9-14] In particular, stimulation of macrophage activation and an increase of phagocytic activity have been shown both in vitro and in animal models.[10, 11] Such effects might be mediated by an increased secretion by monocytes of cytokines such as TNF-α or interleukins 1, 6 and 10.[12,13] It is noteworthy that there is a consensus in the literature about the fact that the cytokine stimulation profile induced by echinacea is of the anti-inflammatory type. This should render its use safe in the context of COVID-19, particularly in its early stages. Echinacea related increases in the number of natural killer cells [14] and stimulation of classic and alternative pathways of complement activation have also been reported.[15] Furthermore, its activity has been proven in vitro and in vivo, against respiratory viruses such as those of influenza, syncytial respiratory virus, and different species coronaviruses.[16] In fact, echinacea have been shown to inhibit in vitro propagation of SARS-CoV-2.[17] Considering all this, it was our aim to study the possible efficacy of echinacea in COVID-19.[18] Therefore, in 2021, in the middle of the pandemic, with a very limited therapeutic arsenal, and after completing a limited retrospective study, we launched the EChinacea and COronavirus -II (ECCO-II) study to evaluate whether a medicinal preparation of echinacea purpurea was clinically effective and safe for COVID-19 mild symptoms.

Materials and Methods

Study design

This was an interventional, multicentre, double-blind, prospective, randomized, controlled clinical trial set up at four public Spanish hospitals (Table 1). The recruitment

took place between July 2021 and June 2022. The study was approved by the Galician Ethics Committee for Research with Drugs (CEIm-G) and the Spanish Agency of Drugs and Sanitary Products (AEMPS). It was registered with EudraCT number 2021-000850-24 and Clinicaltrials.gov identification number NCT04981314.

Participants (inclusion criteria)

We recruited ambulatory patients aged 18 years and above presenting with mild, mostly respiratory symptoms of PCR or antigen test-confirmed COVID-19 disease, at days 1 to 9 of disease were recruited, and having experienced at least one fever episode (defined as a thermometer-measured temperature of ≥ 37 °C). Pregnant or breastfeeding women were excluded from the study, and so were patients with progressive systemic diseases such as tuberculosis, immune system ailments, collagenosis, multiple sclerosis, AIDS, and other immune diseases. Patients having recently received oxygen therapy, or receiving immunotherapy, were also excluded. Finally, patients having received any COVID-19 vaccination were initially excluded. However, in later stages of the trial this exclusion criterium was lifted, given the eventual high vaccination rate reached in Spain. All participants gave written informed consent to the recruiting physician.

Randomization and blinding

Consented participants were assigned by the recruiting physician to either the control arm, receiving standard-of-care treatment and placebo (SOC + P) or the intervention arm, receiving standard-of-care treatment and echinacea (SOC + E) using the random sampling function of the SPSS Statistics package (version 25). The generated lists (one for each participating hospital) were generated by a member of the team that did not participate in the recruiting, and therefore recruiters and participants were blinded.

Drug for treatment

The drug tested, Echinacea Arkopharma, hard caplets, is authorised and commercial in Spain. It is classified as a plant-based drug under the category of "traditional use" by the European Medicines Agency, Art. 16 d(1) of Directive 2001/83/EC, Echinacea purpurea (L.) Moench., radix (EMEA/HMPC/577784/2008), with the following indication: "Traditional herbal medicinal product for supportive treatment of common cold". The product is a traditional herbal medicinal product for use in specified indication exclusively based upon long-standing use.

Interventions

Based on standard clinical practice in our milieu, we defined the SOC treatment for COVID-19 involved control of symptoms with paracetamol and antitussives in the milder cases, antibiotics to treat secondary bacterial infection, dexamethasone in cases of dyspnea, and prophylaxis of thromboembolisms with subcutaneous low molecular weight heparins, as required and based on each individual case. The intervention group (SOC + E) received 1.5 g of cryo-milled root of Echinacea purpurea (L.) Moench per day, as 2 hard caplets of the over-the-counter drug Echinacea Arkocapsules every 8 hours during 7 days, that means 6 g/day. The placebo group (SOC + P) received an equal daily number of hard caplets formulated with the same excipients as the drug caplets and indistinguishable from them.

Study procedures

Patient-related clinical/investigation data, treatment compliance, outcomes and adverse events (AEs) were collected by the site investigators (recruiting physicians) and recorded on the pre-specified electronic case report form. Blood samples were collected and processed on days 1, and 12 ± 3) to measure concentration of hemoglobin, hematocrit, number of polymorphonuclated cells, lymphocytes, monocytes, platelets, and blood levels of C-reactive protein, ferritin, D dimer and AST. The day of recruitment, participants were given a pack containing the treatment (or placebo), a sheet of instructions summarizing those provided by the recruiting physician, a pulse oximeter, and a self-assessment sheet. A questionnaire was administered to them verbally by the recruiting physician (see online supplemental appendix). A follow-up telephone call took place at day 7 (± 1), during which compliance with and completion of the treatment were assessed and a questionnaire presented verbally. The second follow-up session (day 12 ± 3) was a physical visit whenever possible and included blood collection (vide supra). If not possible, it was conducted over the telephone; in any of the two cases, it included a questionnaire (see online supplemental appendix). The final follow-up session (day 28 ± 2) was telephonic in all cases and consisted of a verbal questionnaire (see online supplemental appendix).

Outcomes

The primary outcome, OE1, is days with fever (thermometer-measured axillary temperature of ≥ 37 °C at least once during the day).

The secondary outcomes analyzed were: OE2: days with subjective dyspnea; OE3: days with unsaturation (≤ 96%); OE4: days with disease; OE5: percentage of hospitalizations: OE6: length of hospitalizations; OE7: days of sick leave; OE8: percentage to visits to emergency room; OE9: percentage of admissions to intensive care units; OE10: percentage of deaths; OE11: subjective perception by the recruiting physician of the treatment usefulness to improve the evolution of the disease and OE12: subjective perception by the patient of the treatment usefulness to improve the evolution of the disease.

Statistical analyses

Sample size calculation

From our previous clinical experience, we estimated that the main variable (days with fever) has a standard deviation of 2 days (σ=2). We estimate that its mean value for the placebo group is of 7.5 days (μ1=7,5) and for the experimental group, 5 days (μ2=5). The limit of relevant superiority is estimated in 1.5 days (ε=-1.5). For 100 patients in each group, (n1=100, n2=100), la power obtained is of 96.98% (pow=1-β=0.97) to allow for a conclusion of relevant superiority with a level of significance of 5% (α=0.05). Considering an anticipated dropout rate of 15 %, Recruitment of 230 patients would be necessary. These calculations were carried out with the Ene 3.0 statistical package for calculation of sample sizes.

T-tests or Mann-Whitney tests were performed according to the parametric or non-parametric nature of the data for the groups being compared. For comparison of more than two groups, ANOVA (in case of

parametric value distribution) or Kruskal Wallis tests (in case of non-parametric value distribution) were applied. For continuous variables, t-tests or Wilcoxon tests were applied depending on the parametric or non-parametric distribution of data. For the analysis of contingency tables and to compare frequency proportions and distributions the chi-square or Fisher exacts tests were used adequate. To assess the evolution of a qualitative variable, the McNemar test was used. Confidence intervals of 95% were used as needed for variables related to the general objective and for the main response variables related to specific objectives.

Finally, and in relation with the hypothesis of relevant superiority, in the control arm, the mean of days of fever was determined and the absolute value defined in the protocol for superiority, subtracted. The IC at 95% was calculated for the estimation of the mean of the experimental arm.

Differences were considered statistically significant for p values < 0,05. The SPSS v19 statistical software package was used for all statistical calculations.

Adverse events

For assessment of adverse events, the following safety objectives were evaluated: 1) Incidence of respiratory disease (subjective feeling of dyspnea) and ≥96% desaturation; 2) incidence of palpitations; 3) incidence of increased transaminase levels (AST >3X normality range maximum value); in cadence of headaches; 4) incidence of digestive problems; 5) incidence of insomnia and nervousness.

Public and patient involvement

While patients did not participate in the experimental design, their opinion was collected through evaluation of outcome OE12: subjective appreciation of the usefulness of the product, in the opinion of the patient.

Results

Recruitment, compliance and follow-up

Recruitment was designed as non-competitive, closed by centre (July 2021), and it started that way. However, very soon it became obvious that participation was low, mainly as a consequence of difficulties in obtaining the consent of potential participants. Fewer than 1 in 50 accepted to participate. This was even worse in Barbastro, likely because of socio-demographic reasons (this hospital tends mostly to a scattered, rural, aged population), only 1 in 100 potential participants accepted to enroll in the study, approximately. In the other extreme, recruitment was 100% in the Barbanza hospital, which tends to a more densely populate and urbanized area, which paradoxically had a low incidence of cases.

	Hospital do Barbanza	Hospital de Barbastro	Hospital Clínico Universitario de Santiago	Hospital Clínico de Zaragoza	Total
Planned (n)	15	46	31	138	230
Recruited (n, %)	15 (100 %)	7 (15.2 %)	23 (74.2 %)	54 (39.1 %)	99 (43,0 %)
Completion of treatment/placebo	11	1	15	41	68
Patients with bloodwork completed in two samples	9	0	8	25	42

Table 1: Recruitment

Finally, after 12 months, recruitment was closed in June 2022, with 99 patients, a considerably lower number than the study target of 230. In February 2022 we applied for and were granted permission from the regulatory authority (AEMPS) to also recruit vaccinated patients. This resulted in Recruitment of 5 vaccinated patients in the treatment group and 5 in the placebo group. Of the total number of recruited patients, 67 fully completed the treatment or placebo during at least 6 days. Within such group, 42 participants got the planned bloodwork of two samples. Table 1 summarizes recruitment data and table II the baseline characteristics of the patients. Of the 22 participants that voluntarily dropped out of the study before completion, all reported loss of interest, change of mind, tiredness or personal decision. No voluntary dropouts were caused by adverse events. Of the dropout cases, 10 belonged to the placebo and 12 to the treatment group (p=0,844, n.s).

Within the remaining 67 cases, only two adverse events resulted in interruption of the treatment by the recruiting physician. Both consisted of mild diarrhea (n = 2). These cases do not lead to a statistically significant difference between the treatment and control groups. Since diarrhea is common in Covid-19 patients, we cannot rule out that such was its cause. There was no AST elevation in any case within the treatment and control groups. Two cases of effort-induced tachycardization were recorded in the treatment group, vs none in the placebo group (p=0.344, n.s.). None of these two cases had to be admitted to the hospital or left the treatment, and both felt cured on day 28 of follow up.

Characteristics	All patients (n= 99)	Placebo (n= 49)	Treatment (n= 50)	P value (1)
Age, years (mean ± SD)	35.50 (± 11.9)	35.85 (± 11.1)	35.16 (± 12.8)	0.776 (n.s.)
Feminine gender (nº, %)	50 (51,5 %)	27 (55,1%)	23 (46.0 %)	0.269 (n.s.)
Nationality (nº, %)				
Spanish	70 (71.4 %)	34 (69.4 %)	36 (73.5 %)	
South American [2]	12 (12.2 %)	7 (14.3 %)	5 (10.2 %)	0.82 (n.s.)
Other [2]	16 (16.3 %)	8 (16.3 %)	8 (16.3%)	
Smoking habit (n, %)	10 (10.1 %)	4 (8.2 %)	6 (12.0 %)	0.526 (n.s.)
Vaccinated (n, %)	11 (10,9 %)	6 (13,1 %)	5 (10,0 %)	0,322 (n.s.)

Hypertension	4 (4.0 %)	2 (4.1 %)	2 (4.0%)	0.984 (n.s.)
Diabetes mellitus	4 (4.0 %)	2 (4.1 %)	2 (4.0 %)	0.984 (n.s.)
Chronic obstructive pulmonary disease	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-
Asthma	5 (5.8 %)	2 (5.1 %)	3 (6.4 %)	0.804 (n.s.)
Cancer	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-
Ischemic heart disease	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-
Depression	2 (2.0 %)	0 (0.0 %)	2 (4.0 %)	0.157 (n.s.)
Concomitant treatments (≥30 days) (n, %)				
Neuroleptics	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	-
Antidepressants	4 (4.0 %)	2 (4.1 %)	2 (4.0 %)	0.984 (n.s.)
Benzodiazepines	5 (5.1 %)	2 (4.1 %)	3 (6.0 %)	0.663 (n.s.)
Other	22 (23.7 %)	9 (20.9 %)	13 (26.0 %)	0.566 (n.s.)
Initial COVID-19-related parameters				
Evolution of the disease (days)*	4.0 (2.0 - 6.0)	4.0 (2.0 - 6.5)	3.5 (2.0 - 5.2)	0.235 (n.s.)
Actual temperatura (ºC) (mean ± SD)	36.998 (± 0.935)	36.967 (± 0.822)	37.027 (± 1.043)	0.756 (n.s.)
Maximum temperature reached (ºC) (mean ± SD)	37.695 (± 3.887)	37.105 (± 5.533)	38.234 (± 0.813)	0.170 (n.s.)
Dyspnea (n, %)	40 (40.4 %)	19 (38.8 %)	21 (42.2 %)	0.744 (n.s.)
Days with feeling of dyspnea*	0.00 (0.00 - 2.25)	0.00 (0.00 - 3.00)	0.00 (0.00 - 2.00)	0.784 (n.s.)
Current saturation*	98.00 (97.00 - 99.00)	98.00 (97.00 - 99.00)	98.00 (97.00 - 99.00)	0.226 (n.s.)
SAP (mean ± SD)	127.57 (± 17.600)	127.29 (± 17.070)	127.87 (± 18.374)	0.882 (n.s.)
DAP (mean ± SD)	79.09 (±10.666)	80.39 (±11.081)	77.68 (±10.158)	0.263 (n.s,)
Respiratory frequency*	14.00 (12.00 - 14.00)	14.00 (12.00 - 14.00)	13.00 (12.00 - 14.00)	0.253 (n.s.)
Received dexamethasone (n, %)	1 (1.0 %)	1 (1.0 %)	0 (0.0 %)	0.315 (n.s.)
Received subcutaneous heparin (n, %)	0 (0.0 %)	0 (0.0)	0 (0.0 %)	-

Table 2: Baseline characteristics of patients.

(1) Student´s t test; (n.s.) = non-significant. (2) migrant residents. SAP: systolic blood pressure. DAP: diastolic blood pressure

Primary outcome

The number of days with fever (thermometer-measured axillary temperature of ≥ 37 °C at least once during the day) of the control (placebo) group was of 4,76 ± 2,849, compared to 3,81 + 2,558 of the treatment group. The difference was not statistically significant as per the Student´s t test, which was applied after normal distribution of both data distributions was confirmed (Table III).

Secondary outcomes

None of the variables associated with the eleven secondary outcomes of the study reached statistical significance when data for the treatment and placebo groups were compared. Thus, the number of days with subjective dyspnea was 3.74 ± 4.48 vs. 3.41 ± 4.79 for the treated (n = 31) vs. placebo (n = 29) group (p = 0.785). Saturation was 97 ± 76 % vs. 97 ± 96, for the treated (n = 29) vs. the placebo group (n = 25), respectively (p = 0,670). The number of days with disease was 10 ± 8.8 vs. 11 ± 2.3, for the treated (n = 25) vs. the placebo (n = 23) group (p = 0.753). All of these variables had normal distributions (Table III).

There was one hospitalization in each group. The case in the treatment group was a 30-year-old female whereas the case in the placebo group was a 34-year-old male. None of them had previous risk factors and both were admitted with a bilateral pneumonia. They were released after a few days of hospitalization. As a consequence of logistical reasons, the exact lengths of hospitalizations are unfortunately not recorded and it is impossible to track a posteriori due to the blinding.

With regard to the number of participants that required sick leave, in the treatment group, 14 of 24 (58,3%) did, whereas in the placebo group, the number was 17 of 23 (73%). While the number is higher in the placebo group, the difference did not reach statistical significance as determined by Pearson´s Chi squared test (p = 0.260).

	Treated (n)	**Duration, days (mean ± standard deviation)**	**Placebo (n)**	**Duration, days (mean ± standard deviation)**	**P value**
OE1: Days with fever (temperature ≥ 37ºC at any time of the day	29	4.76 ± 2.85	27	3.81 ± 2.56	0.199 **(1)** (n.s.)
OE2: Days with subjective dyspnea	31	3,74 ± 4,48	29	3,41 ± 4,79	0.785 **(1)** (n.s.)
	Treated (n)	**% Of O_2 saturation (mean ± standard deviation)**	**Placebo (n)**	**% Of O_2 saturation (mean ± standard deviation)**	**P value**
OE3: Saturation at day 14	29	97 ± 76	25	97 ± 96	0.670 **(1)** (n.s.)

	Treated (n)	Duration, days (mean ± standard deviation)	Placebo (n)	Duration, days (mean ± standard deviation)	P value
OE4: Days with disease	25	10 ± 8.8	23	11 ± 2.6	0.753 **(1)** (n.s.)
	Treated (n)	**Hospitalised**	**Placebo (n)**	**Hospitalised**	**P value**
OE5: Hospitalizations	35	1 case	33	1 case	1.000 **(2)** (n.s.)
OE6: Length of hospitalization	35	(n.a.)	33	(n.a.)	(n.a.)
OE7: Have you had a sick leave from work?	24	14 (58,3%)	23	17 (73%)	0.260 **(3)** (n.s.)
OE8: Have you been admitted to the emergency room anytime throughout these last 28 days?	26	3 (11%)	24	5 (20,8%)	0.456 **(2)** (n.s.)
OE9: Admited to intensive care?	35	0 cases	33	0 cases	n.s.
OE10: Deaths	35	0 cased	22	0 cases	n.s.
	Treated (n)	**Mean rank**	**Placebo (n)**	**Mean rank**	**P value**
OE11: Do you feel that the caplets were efficacious to treat the patient? (question to physician)	16	19.41	16	13.59	0.063 **(3)** (n.s.)
OE12: Do you feel fully recovered? (question to patients)	26	25 (96,2%)	24	21 (87%)	0,340 **(3)** (n.s.)

Table 3: Outcomes.

(1) Student´s t test; (2) Fisher´s exact test; (3) Pearson´s Chi squared; (n.s.) = non-significant. (n.a.) not available

The same was true for the number of participants that were admitted again at the emergency room during the course of the study: 3 of 26 (11%) in the treatment group and 5 of 24 (20,8%) in the placebo group (p = 0.456).

No referrals to intensive care units and no deaths were registered in any of the two groups. Finally, with respect to the subjective appreciation of the usefulness of the product, in the opinion of the recruiting physician (O11), the mean rank of responses was of 19.41 and 13.59 for the treatment and placebo groups, with a positive trend that nevertheless did not reach statistical significance as determined by Pearson´s Chi squared test (Table III). With respect to the opinion of the patient (O12), 96.2% of patients in the treatment group vs. 87% in the placebo group reported feeling completely recovered at day 28, again a difference in the direction of effectiveness that did not reach statistical significance (Table III).

With respect to the analytical parameters, plasma ferritin levels were of 189,2 ± 194,3 mg/L for the treated (n = 20) vs. 379 ± 538 for the placebo (n = 18) group. While there is a clear trend of an effect of the treatment to decrease the ferritin levels at day 14, the difference did not reach statistical significance (p = 0,148) (Table IV). Also, no statistically significant differences were found in values of blood total leukocytes, and D dimer (data not shown).

	Treated (n)	Normal ferritin values (<150 mg/L) (n,%)	Placebo (n)	Normal ferritin values (<150 mg/L) (n,%)	P value
Ferritin (normal/altered)	20	11 (55%)	18	6 (35%)	0,231 **(1)** (n.s.)
	Treated (n)	**Mean ± SD**	**Placebo (n)**	**Mean ± SD**	**P value**
Ferritin (mg/L)	20	189,2 ± 194,3	18	379 ± 538	0,148 **(2)** (n.s.)

Table 4: Blood ferritin values at day 14.

Discussion

This study is the first prospective, multicentre, randomised, controlled clinical trial investigating the clinical efficacy and safety of drug-grade Echinacea purpurea caplets to treat mild, respiratory acute COVID-19 infection. The dosage chosen that recommended by the manufacturer for use with viral respiratory infections. The study showed that a treatment course of 7 days added to the standard care treatment (steroids, anticoagulants, and antibiotics), did not influence the primary outcome of the trial, i.e., days with fever, nor the secondary efficacy outcomes. On the other hand, the medication appeared to be safe and well tolerated with no severe AEs attributable to it; just two cases (3%) of mild diarrhea were reported, a number that did not reach statistical significance and that could be perhaps attributed to the disease itself. This multicentre trial advances the evidence base on the potential impact of Echinacea purpurea on mild respiratory COVID-19 infection. Echinacea purpurea was a potentially attractive therapeutic choice from previous preclinical and clinical experience, [18,19] as numerous randomised, controlled clinical trials have been carried out to evaluate the effect of different preparations of echinacea as a treatment of acute viral infections of the respiratory tract after the inception of symptoms. In their classic revision, Block and Mead report that 12 studies showed a significant decrease in the duration and/or severity of disease treated with echinacea.[6] In contrast, 4 of the reviewed studies showed a lack of statistically significant effect, although in two of these there as a positive trend.[6] In turn, the systematic revision of treatment and prevention studies by Giles et al. concluded that 13 de 15 of them showed efficacy.[20] As with all phytotherapy studies, a key

difficulty when comparing studies is the fact that often different preparations are used, although there seems to exist a solid evidence in favor of the effectiveness of echinacea for the treatment of common colds. In this context, the lack of any statistical significant effect in the current study was disappointing, and given some trends, we believe that one key reason is the lack of statistical power resulting from the substantially low recruitment, which did not meet the number we had calculated as needed (see Materials and Methods). This failure to meet the recruitment number target is in fact the main limitation of our study. In particular, we found trends in favor of the treatment in lower serum ferritin values (Table IV), subjective opinion on the effectiveness of the treatment, as reported by both the recruiting physician and the patient, percentage of patients who needed sick leave, and number of visits to the emergency room throughout the 28 follow up days (Table III). In this respect, it is noteworthy to compare our results with those of the study by Kolev et al., that was published while we were finalizing our manuscript. [21] A randomized, open, controlled, exploratory clinical study was conducted after the peak of the pandemic to evaluate the effect of a commercial preparation of Echinacea purpurea extract to prevent and treat viral respiratory tract infections in general and SARS-Cov-2 infections in particular. [21, 22] Studying 120 initially healthy volunteers, the authors found a statistically significant prophylactic effect of the treatment with respect to detection of the SARS-CoV-2 virus in nasopharyngeal and oropharyngeal swabs, with 5 and 14 SARS-CoV-2 positive detections in the treated and control groups, respectively. The corresponding relative risk for SARS-CoV-2 infection was of 0.369 and 0.768, respectively. On the other hand, despite this definitive proof of effectiveness, the effect of the treatment to reduce the risk of clinical respiratory covid-19 infection did not reach statistical significance, a consequence, according to the authors, of the small number of cases, given that only every third virus infections turned into a symptomatic episode. [21] Also, while the time to completely clear the virus was reduced by ~30%, the effect did not reach statistical significance, again, a consequence of the small number of cases (5 episodes in the treatment group and 8 in the control group). No data on the effect of the treatment on the clinical course of the disease were reported. [21] While any comparison needs to be done with extreme caution, given the different formulations of the products used, the outcomes of the study by Kolev et al. and the current study underscore the difficulty posed by underpowered recruitment; however, the study of Kolev et al. demonstrates, without doubt, a positive effect of echinacea in reducing SARS-CoV-2 in vivo, in good agreement with previous studies showing an effect in cellula. [17,23] It is tempting to speculate that with a higher number of cases, statistical significance might have been reached also for prevention of clinical disease and reduction of clinical signs and/or duration. We did not measure virus clearance for logistical reasons -our study was conducted in the middle of the pandemic, under conditions of an overstretched emergency care-, so it remains to be seen whether a similar effect might have occurred. Our low sample does not allow us to rule out the possibility that the treatment might be useful in a subset of patients as a consequence of a putative interaction of the active principles with the characteristics of the immune system of individual patients, some of which may have benefitted more than others. Furthermore, our recruited population was young (35.50 ± 11.9 years); it is conceivable that an older population might have benefitted more from the immune system boosting properties of echinacea.

Conclusions

Echinacea purpurea, in its pharmacological presentation known as Echinacea Arkopharma, presents a good safety profile for its use in mild COVID-19, with a very low incidence of adverse effects, when used as a putative coadjuvant in the treatment of mild COVID-19. In this study, in the context of a low recruitment that reached only 20% of our objective, it did not show an effect in the clinical parameters of the COVID-19-induced acute respiratory infection. However, some positive trends were seen. Further studies are warranted.

Acknowledgments

We thank all study participants. JLPA thanks all members of the traditional music schools of Graus and Benavarri, Jesus S. and the Tirurirus Free traditional music band for inspiration and support to conceive and conduct this study during difficult times

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding

This research received no funding.

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DOI:10.31579/2690-4861/651

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