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Randomized trials - Ivermectin repurposing for COVID-19 treatment of outpatients with mild disease in primary health care centers

Ensaio aleatório - Reutilização de Ivermectina para tratamento COVID-19 de pacientes ambulatórios com doença leve em centros primários de saúde

Ensayos aleatorios - Reutilización de la Ivermectina para el tratamiento con COVID-19 de pacientes ambulatorios con enfermedad leve en centros de atención primaria

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Abstract
Objective: to evaluate the therapeutic intervention with Ivermectin in outpatients with COVID-19 mild disease, to increase medical discharge and prevent the progression to moderate or severe disease. *Methods*: Randomized Trial, n= 254. The subjects were divided into experimental (EG: n= 110) and control groups (CG: n= 144). The EG received Ivermectin orally 0.6 mg/kg weight in two doses. All participants were by physical examination COVID-19 diagnosed with negative RT-PCR at the beginning and the end of protocol. Differences between the variables were determined using the Chi-square test ($p<0.05$). The contagion risk (Odds Ratio) was calculated using software STATA. *Result*s: Both groups were similar in age, sex, and comorbidities. A significant reduction in the percentage of participants with symptoms (PPS) was observed in the EG and CG when the clinical evaluation of symptoms was performed from 5th to 9th day ($p= 0.0005$). When the clinical evaluation was performed from 10th to 14th day there was no significant difference. A higher proportion of medical discharge was observed in EG (98.2%) vs. CG (86.1%) ($p= 0.0007$). EG showed 8 times more chance of receiving medical discharge than CG (OR 8.71, 95% CI: 1·99 – 38.12, $p= 0.004$). The

treatment effect with Ivermectin to obtain medical discharge from outpatient care was analyzed by logistic regression. Then, the chance to obtain medical discharge was independent of variables sex, age, and comorbidities. *Conclusion*: This work supports the potential efficacy of Ivermectin in outpatient care with mild COVID-19 as a potentially useful intervention of public health consideration.
Keywords: COVID-19; Ivermectin; Outpatient care; Drug repurposing; Primary Health Care.

Resumo

Objetivo: avaliar a intervenção terapêutica com Ivermectina em pacientes ambulatoriais com doença leve de COVID-19, para aumentar a alta médica e prevenir a progressão para doença moderada ou grave. Métodos: Ensaio Randomizado, n= 254. Os sujeitos foram divididos em grupo experimental (GE: n= 110) e grupo controle (GC: n= 144). O GE recebeu Ivermectina oral 0,6 mg/kg de peso em duas doses. Todos os participantes realizarão exame físico COVID-19 e diagnosticados com RT-PCR negativo no início e no final do protocolo. As diferenças entre as variáveis foram determinadas pelo teste Qui-quadrado ($p<0,05$). O risco de contágio (Odds Ratio) foi calculado por meio do software STATA. Resultados: Ambos os grupos foram semelhantes em idade, sexo e comorbidades. Uma redução significativa no percentual de participantes com sintomas (PPS) foi observada no GE e GC quando a avaliação clínica dos sintomas foi realizada do 5º ao 9º (p= 0,0005). Quando a avaliação clínica foi realizada do 10º ao 14º dia não houve diferença significativa. Foi observada Maior proporção de alta médica no GE (98,2%) vs. GC (86,1%) (p= 0,0007). O GE apresentou 8 vezes mais chance de receber alta médica do que o GC (OR 8,71, IC 95%: 1,99 – 38,12, p= 0,004). O efeito do tratamento com Ivermectina para obter alta médica da assistência ambulatorial foi analisado pela regressão logística. Então, a chance de obter alta médica foi independente das variáveis sexo, idade e comorbidades. Conclusão: Este trabalho apoia a eficácia potencial da Ivermectina na assistência ambulatorial com COVID-19 leve como uma intervenção potencialmente útil de saúde pública.
Palavras-chave: COVID-19; Ivermectina; Assistência Ambulatorial; Reposicionamento de medicamentos; Atenção Primária à Saúde.

Resumen

Objetivo: evaluar la intervención terapéutica con Ivermectina en pacientes ambulatorios con enfermedad leve de COVID-19, para aumentar el alta médica y evitar la progresión a enfermedad moderada o grave. Métodos: Ensayo aleatorio, n= 254. Los sujetos se dividieron en grupos, experimental (GE: n= 110) y control (GC: n= 144). El GE recibió Ivermectina vía oral 0,6 mg/kg de peso en dos dosis. Los participantes fueron diagnosticados por examen físico COVID-19 y RT-PCR negativa al principio y al final del protocolo. Las diferencias entre variables se determinaron mediante prueba de Chi-cuadrado ($p<0,05$). El riesgo de contagio (Odds Ratio) se calculó utilizando el software STATA. Resultados: Ambos grupos fueron similares en edad, sexo y comorbilidades. Se observó una reducción significativa del porcentaje de participantes con síntomas (PPS) en ambos grupos cuando la evaluación clínica de los síntomas se realizó del 5º al 9º día (p= 0,0005). Cuando la evaluación clínica se realizó del 10º al 14º día no hubo diferencias significativas. Se observó una mayor proporción de altas médicas en el GE (98,2%) frente al GC (86,1%) (p= 0,0007). El GE mostró 8 veces más chances de recibir alta médica que el GC (OR 8,71, IC 95%: 1-99 - 38,12, p= 0,004). El efecto del tratamiento con Ivermectina para obtener alta médica de atención ambulatoria se analizó mediante regresión logística. La chance de obtener alta médica fue independiente de las variables sexo, edad y comorbilidades. Conclusiones: Este trabajo apoya la potencial eficacia de la Ivermectina en la atención ambulatoria con COVID-19 leve como una intervención de consideración en salud pública.
Palabras clave: COVID-19; Ivermectina; Atención ambulatoria; Reposicionamiento de medicamentos; Atención primaria de salud.

1. Introduction

Since the beginning of the pandemic, despite drastic containment measures, the spread of COVID-19 has threatened to collapse health systems around the world, and also had devastating socioeconomic consequences worldwide (Carvallo, et al., 2020; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). The impact of the coronavirus pandemic has disproportionately affected developing countries whose economies are less able to cope with the new challenges imposed (Bottann et al., 2020; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

International health authorities have focused on the rapid diagnosis and isolation of patients, as well as the search for therapies capable of counteracting the most serious effects of the disease, which constitute approximately 15% of the cases according to WHO (Wu, et al, 2020; WHO 2020; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). Due to the number of infections continues to increase exponentially, the development of vaccines and new antiviral therapies are crucial. While vaccines have been approved for their use, difficulties in responding to high demand and logistical

complexities that accentuate potential inequality must be considered. Hence, repurposing pharmaceuticals remains an important strategy to tackle COVID-19. In this context, the repositioning of drugs currently available on the market with established safety profiles that are implemented on other therapeutic indications, based on solid preclinical studies, is imperative. This is a pragmatic strategy, a faster and cheaper option compared to the new drug development that has proven successful for many medications and can be a key tool in emergencies such as the current one that requires a quick action (Chong, et al, 2007; Ashburn, et al, 2004; Liu, et al., 2013; Dyall, et al., 2014; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). This strategy becomes more relevant in those economies that do not have the necessary resources for the development of new therapies, as in the case of Latin-American countries. In addition, the COVID-19 anti-vaccine movements that have recently become known in these countries (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

Ivermectin is a broad-spectrum antiparasitic agent that has been shown to have antiviral activity against a wide range of viruses. Caly et al. (2020) suggested that Ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2 (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). In line with this study, numerous clinical trials, especially from developing countries, are evaluating the potential of Ivermectin against COVID-19 with results that are not conclusive yet regarding its efficacy and safety (Cassrá, 2020; Chahla, et al., 2021; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv; Ministerio de Salud de Tucumán I.D.D.E.A – TUC. 2020; Krolewiecki, et al., 2020; Elgazzar, et al., 2020).

The World Health Organization (WHO) published in 2016 the Guide for the Management of Ethical Issues in Outbreaks of Infectious Diseases, which emerged based on the response to the Ebola virus disease outbreak in West Africa in 2014 and it was called "Monitored Emergency Use of Unregistered and Experimental Interventions' (MEURI). It is intended to complement existing guidelines on ethics in public health in situations of great uncertainty and include recommendations for the use of unproven interventions outside of clinical trials (WHO, 2014).

As well as mentioned by Mayer, et al., 2022, "MEURI interventions are applied when there are no treatments of proven efficacy, it is not possible to start clinical trials immediately, existing preliminary data support the intervention, the relevant regulatory, ethical and scientific authorities approve such use, resources are available to minimize risks and Informed consent is obtained from the patient".

In Argentina's health system, the emergency of COVID-19 requires the urgent development of strategies to avoid the impact of the disease on our population, prevent the saturation of the health system and allow us to carry out adequate treatments to reduce the mortality of the disease. In this context, our health system considered the study of the repositioning of Ivermectin as a strategy to prevent the progression to moderate or severe stages of COVID 19 disease since it is a safe drug, which is available in our environment and with antecedents in other health systems in the world of its use both in treatment and prevention (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

This study aims to evaluate the therapeutic intervention with Ivermectin in outpatients with COVID-19 mild disease, to increase medical discharge and prevent the progression to moderate or severe disease.

Primary Outcome. Increase medical discharge from outpatient care with COVID-19 mild disease.

Secondary Outcomes. Decrease the percentage of participants with symptoms (PPS) from outpatient care.

2. Methodology

2.1 MEURI Program for the use of Ivermectin in COVID-19 patients

The Ministry of Health of the Province of Tucumán (Argentina) authorized the implementation of a MEURI Program based on the use of Ivermectin (600 μg/kg) in COVID-19 adult patients (older than 18 year-old).

2.2 Participants

The total group n= 254 enrolled outpatients care. The study was conducted between September 2020 to January 2021. The health coverage service was administered by the Health System of the State of Tucumán (SI.PRO.SA, Tucumán, Argentina). The people who agreed to participate in the study gave their informed consent before starting the study (Independent Ethical Committee / Health Research Directorate, Ministry of Health, Tucumán Government, Argentina, IRB: 054/2020 in accordance with the ReNIS, National Register in Health Research, Argentina /0032). The clinical trials registry number is NCT04784481. This study conforms to all CONSORT guidelines and reports the required information accordingly (see Supplementary Checklist).

2.2.1 Inclusion criteria

- Over 18 years of age of any sex.
- Outpatients infected by SARS-CoV-2 confirmed by positive RT-PCR test.
- Women of childbearing age with a negative pregnancy test.
- Mild disease-patients with two or more of the following symptoms: fever less than 38·5°C and higher than 37.5°C according to Ministry of Health, Argentina (Ministerio de Salud de Nación, 2020), isolated diarrheal episodes, hyposmia or hypogeusia, mild desaturation (between 96 and 93%), dyspnea, polyarthralgia, persistent headache, abdominal pain, erythema of the kidney, nonspecific rash.

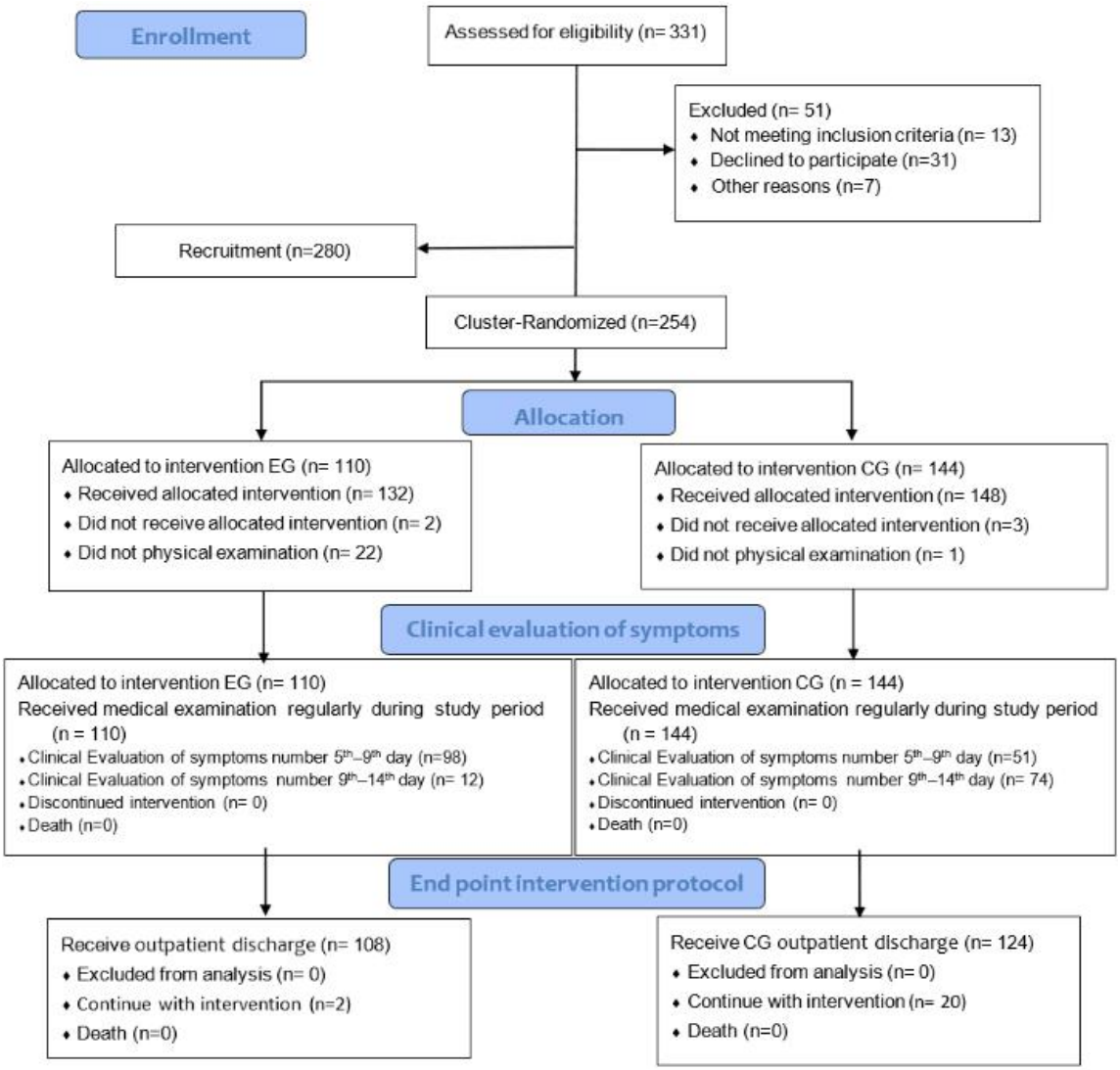
2.2.2 Exclusion Criteria

- Hypersensitivity or allergy to Ivermectin.
- Pregnant or lactating.
- Children or adolescents under 18 years of age.
- Patients with neurological pathology, renal insufficiency, hepatic insufficiency.
- Weight less than 40kg.
- Patients with concomitant use of drugs that act on GABA, barbiturate and benzodiazepine receptors.
- Patients who have not completed / signed the informed consent.

2.3 Randomization and masking

Randomized trials. Participant centers depend on Public Health System of Tucumán, Argentina. Each of the health centers was randomly assigned to receive or not the intervention under study. Outpatients with mild COVID-19 disease were randomly assigned to the Experimental Group (EG) and Control Group (CG). Staff of each assistance center knew what intervention was being implemented as well as patients. Data processing group was blind to analyze the database (Chahla et el., 2021 Clinical Trials).

Figure 1. Consort flow diagram.



Source: Authors' own diagram.

Figure 1 shows the CONSORT flow diagram. Note that 331 patients were initially assessed for eligibility, n= 280 recruited, and allocated to this study n= 254 distributed in EG (n= 110), and CG (n= 144). The clinical evaluation of symptoms considered for a 1st time frame was carried out from 5th to 9th day, this is since the effects of the treatment can manifest around 7 days (±2) and whereas it is the period during which the disease may progress to more serious stages, being evaluated in this instance in EG (n= 98) and CG (n= 51) (Zhou, et al., 2020; Rubin &Crowe. 2020). Patients were reviewed too in a 2nd time frame: from 9th to 14th day EG (n= 12), and CG (n= 79).

2.4 Intervention Protocol

Participants were assessed at the beginning of the program with a medical history and a brief physical examination. Outpatients who agreed to receive oral treatment with Ivermectin were referred to as the Experimental Group (EG) and those who did not were referred to as the Control Group (CG).

The EG received protocol Ivermectin orally 4 tablets of 6 mg= 24 mg every 7 days for 4 weeks plus symptomatic treatment (500mg paracetamol every 6 or 8h, no more than 4 tablets daily; 100mg aspirin, 1 tablet per day with breakfast; 150mg Ranitidine, 1 tablet in the morning, and 1 tablet at night). The CG received only symptomatic treatment. Patients with

comorbidities continued with the basic medication for the underlying pathology (see description in results section). All participants were evaluated by physical examination and COVID-19 infection was diagnosed with positive RT-PCR. Clinical evaluation of symptoms was carried throughout the study period. Enrolled subjects completed symptom questionnaires (including reporting of any adverse effects of treatment), physical examinations and remote clinical telemedicine follow-up and received medical discharge 4 weeks after the start of the intervention (Chahla et al., 2021 Clinical Trials.

The 10-category ordinal scale recommended by the WHO was used to classify patients according to clinical patient state: ambulatory mild disease, moderate disease, severe disease (Marshall, et al., 2020).

2.5 Security definitions

An Adverse Event (AE) was defined as any medical event, sign, symptom, or disease temporarily associated with the use of the medication, which could occur in the subjects enrolled in the study (WHO, 2009).

2.6 Adherence to treatment

WHO defines adherence to treatment as compliance with it; that is, taking the medication according to the dosage of the prescribed schedule; and persistently taking the medication over time (Osterberg &Blaschke, 2005). We quantify adherence to treatment through weekly controls that include drug administration and a clinical questioning which includes the report of adverse events. Adhesion tests like Hermes, Morisky and Green have not been used, since they have been designed for treatment of chronic diseases with daily drug intake (Rodriguez Chamorro, et al., 2008). Physicians in charge of each health care center were responsible for the accompaniment during the trial.

2.7 Statistics

Demographic characteristics of the two groups (EG and CG) were summaries with frequencies and percentages, and continuous variables with median and interquartiles. Differences between the categorical variables were estimated using the Chi-square test. The proportion test was applied to compare the proportion of participants with symptoms. Logistic regression was used to model the odds of medical release by sex, comorbidities and age (Odd Ratio: OR). The level of statistical significance was reached when $p < 0.05$. Analysis were performed using STATA 11.2.

3. Results

Demographic profile

In total, n= 254 were enrolled by cluster-randomized for this study. The subjects were divided into experimental (EG: n= 110; median= 40.0 years old, min= 18.0, max= 75.0, 56 female) and control groups (CG: n= 144; median= 36 years old, min= 18.0, max= 71.0, 77 female), $p > 0.05$. Table 1 shows the demographic profile and descriptions of comorbidity for the experimental and control group.

Table 1. Demographic profile.

Variables	Experimental Group (n= 110)	Control Group (n= 144)
Demographic profile		
Median Age (in years)	40	36
Interquartile Range (IQR)	[IQR_{25}: 19; IQR_{75}: 53]	[IQR_{25}: 29; IQR_{75}: 48]
Gender - n°. (%)		
Female	56 (50.91%)	77 (53.47%)
Male	54 (49.09%)	67 (46.53%)
Co-morbidities - n°. (%)		
HTA	14 (12.73%)	18 (12.50%)
DBT	9 (8.18%)	7 (4.86%)
Obesity	8 (7.27%)	4 (2.78%)
>60 years	12 (10.91%)	7 (4.86%)
Asthma	1 (0.91%)	2 (1.39%)

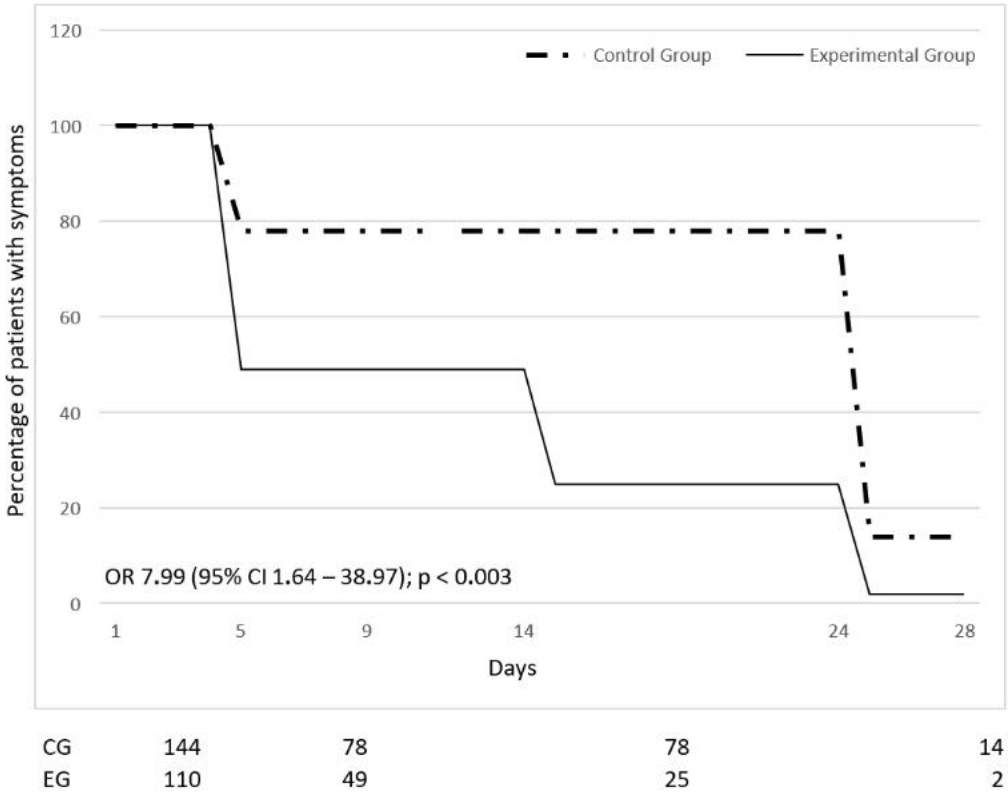
HTA: Hypertension; DBT: Diabetes; Asthma. (*) $p < 0.05$. Source: Authors.

There were no significant differences in baseline characteristics between the experimental and control group. It was observed the following frequency of HTA, DBT, and obesity in the EG relationship to CG; 14:18, 9:7, and 8:4, respectively, however, this difference was not significant. Of the CG patients, 20% (29/144) had some comorbidity, of which 65.5% (19/29) were under medical treatment. 31% (9/29) reported taking ENALAPRIL, 20.7% (6/29) METFORMIN and 13.8% (4/29) LOSARTAN. Of the EG patients, 30.9% (34/110) had some comorbidity of those referred to at work, of these patients, 38.2% (13/34) reported being under medical treatment. 14.7% (5/34) took ENALAPRIL, 8.8% (3/34) METFORMIN, 5.9% (2/34) LOSARTAN, and 8.8% (3/34) other medicines.

Decreased number of patients with symptoms at 5th - 9th day, and posterior

Figure 2 demonstrates a greatest decrease of PPS from the 5th to 9th day, considering the relation between the number of patients with symptoms and the number of patients clinically evaluated: in EG 48/98 and in CG 40/51. Proportion test presented significant differences inter-group $p = 0.0005$. Intra-group the difference was significant same in both group ($p = 0.0001$). Additionally, the difference is higher in EG (51%) vs. CG (21.6%). After the date reported, from 10th to 14th day the medical examination did not show a significant difference between groups. In the 2nd time frame was observed significate different only intra-group EG ($p = 0.0187$).

Figure 2. Kaplan-Meier plot. Percentage of patients with symptoms: i) Enrollment, ii) 1st time frame from 5th to 9th day; iii) 2nd time frame from 10th to 14th day.



Source: Authors.

The association test between the sex variable in both groups showed that there are no significant differences between 1st time frame and 2nd time frame. The same happened when the age variable was included.

Table 2 shows the clinical profile of COVID-19 symptoms in the 1st time frame. The symptoms were divided in two categories: I) systemic symptoms and, II) upper airways symptoms.

Table 2. Symptom's description 1st time frame.

	Control Group			Experimental Group		
Symptoms	**Enrollment**	**1st Time Frame**	***p***	**Enrollment**	**1st Time Frame**	***p***
	I. Percentage Systemic Symptoms in COVID-19					
Fever	38.2	7.5	0.0000	55.5	8.3	0.0000
Diarrhea	25.0	5.0	0.0000	21.8	20.8	0.0145
Polymyoarthralgia	13.9	2.5	0.0000	40.9	16.7	0.0000
Headache	46.5	22.5	0.0000	43.6	16.7	0.0000
Body pain	34.7	2.0	0.0000	17.3	6.3	0.0006
Abdominal pain	9.7	2.5	0.0007	4.5	10.4	0.98
Dyspnea	6.9	2.5	0.0062	6.4	8.3	0.353
Tiredness	16.7	5.0	0.0000	8.2	6.3	0.079
	II. Percentage Upper airway symptoms in COVID-19					
Taste and/or smell disturbance	41.0	55.0	0.0000	34.5	20.8	0.0000
Odynophagia	16.0	2.5	0.0000	15.5	0	*
Cough	17.4	27.5	0.0175	19.1	20.8	0.0438

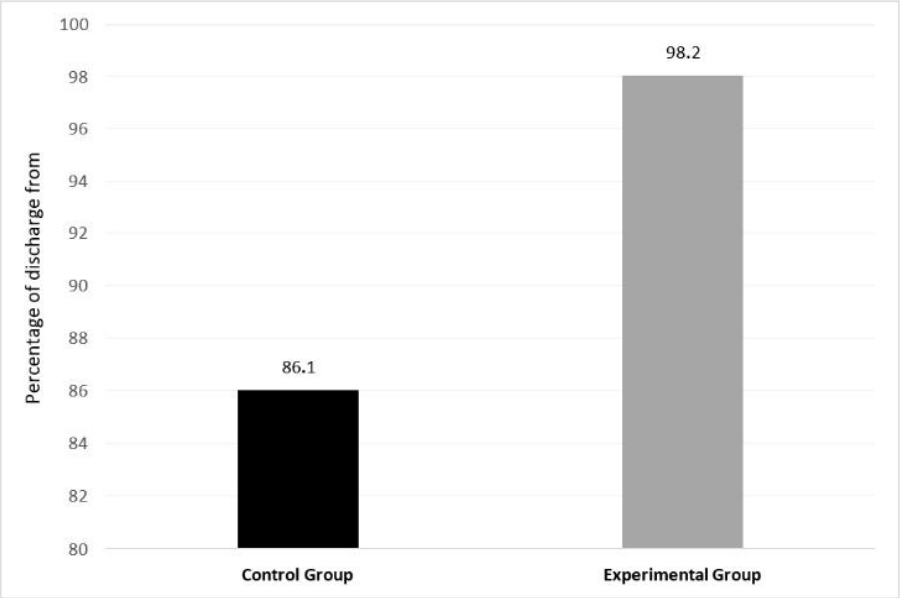
Source: Authors.

There was a decrease in the percentage of systemic and upper airways symptoms reported in the medical examination in both groups (Table 2). It was observed in the systemic symptoms that in both groups there is a favorable response to conventional treatment and to Ivermectin treatment. However, Ivermectin treatment was found to be more effective in alleviating upper airway symptoms, with a significant drop in cough ($p = 0.05$). The proportion test showed that the difference in symptom reduction was in favor of EG with regard to taste and/or smell disorder ($p = 0.00001$)

Discharge of clinic at 28 days after enrollment

The second finding of this study was the number of patients who received medical discharge at 28 days after enrollment (Figure 3)

Figure 3. Medical discharge at 28 days after enrollment.



Source: Authors.

Because of the treatment, the EG had a higher medical discharge than the CG. Proportion was EG: n= 108/110; CG: n= 124/144, *p*= 0.0007. It was observed that there are no differences in achieving medical discharge when adjusting for the age of the patient, both for the median age and for the distribution of interquartile. Similar results were observed for sex distribution. It should be noted that no deaths were reported and no patient left the intervention. Moreover, most of the participants were medical discharged from EG (n= 108), and for CG (n= 8), the rest continued under treatment and observation.

Bivariate analysis and Logistic regression

Bivariate analysis showed 8 times more chance of receiving medical discharge in EG than CG (OR= 7.99, 95%, 1.64 - 38.97, *p*= 0.003). When adjusting for age, sex and comorbidities the odds of medical discharge was maintained in EG (OR= 8.71, CI = [1.99, 38.12]; *p*= 0.004) (Table 3).

Table 3. Logistic regression.

Variables	Odds Ratio	CI (95%)		*p*
Ivermectin	8.71	1.99	38.12	0.004
Comorbidities	0.80	0.45	1.43	0.455
Sex	2.07	0.81	5.26	0.127
Age	1.02	0.98	1.06	0.237

Source: Authors.

4. Discussion

This study was designed to evaluate the potential of Ivermectin as a repositionable drug, for the treatment of mild cases of COVID-19. The results obtained from this intervention suggest a significant positive clinical impact, which deserve to be considered as a potential tool for the management of outpatients with COVID-19.

Currently, many studies about Ivermectin and its potential against SARS-CoV-2 are complete or in development. A pilot study that evaluates the effect of early treatment with Ivermectin for COVID-19, sheds some light on the potential of Ivermectin in a tendency to lower viral loads and lower IgG titers (Chaccour, et al., 2021; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). Other work, either from Argentina shows a faster viral clearance in treated participants (Krolewiecki, et al., 2020; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). Chaccour, et al. (2021) reported that patients treated with Ivermectin experienced a significant diminution of 50% anosmia/ hyposmia than those in the placebo group (76 vs. 158 patient-days of anosmia/hyposmia). The Ivermectin group also reported 30% fewer coughs (68 vs. 97 patient-days of cough). However, in this study, there were no major differences between Ivermectin and placebo in the reported patient days of fever, general malaise, headache, or nasal congestion (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

In line with these results, in our study, outpatients report a significant drop in the percentage of upper airway symptoms in COVID-19 (taste and/or smell disturbance, odynophagia, cough), see Table 2. Concomitantly, the results reported here show that the use of Ivermectin produces a decrease in the number of symptoms reported by patients, such as fever and diarrhea, but above all, a significant decrease in taste and smell loss, which is related to the effects of viral load on upper air vials in patients with mild COVID-19. No patient from either group progressed to severe disease (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

Recently, Lopez Medina et al. (2021) published a study of Ivermectin concerning the time resolution of symptoms in mild patients. Although they do not recommend the use of Ivermectin as a treatment for COVID-19, there are some similarities (and differences) with the results of the present study. We agree that there are no significant differences between both groups at 14 days (see Figure 2), but our main finding shows that the effect of treatment is observed between 5 and 8 days after the patient starts treatment. This difference may be due to the administration of the dose, which in our case is weekly and not daily (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

In addition, Ivermectin was administered on an empty stomach, as indicated by the manufacturer, which probably prevented maximizing the oral bioavailability of this highly lipophilic drug (Caly, et al., 2020; Edwards, et al., 1988). The clinical follow-up of the patients was carried out in person in the Primary Health Centers, which is more accurate concerning symptom recording (Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

There are results that provide evidence of the potential benefit of early intervention with Ivermectin for the treatment of patients diagnosed with mild stages of COVID-19, as Elgazzar et al. (2020) trial. Many studies present the potential of Ivermectin for a viral load reduction, as has been suggested by Caly et al. in vitro. This could have the potential effect on disease progression and spread (Caly, et al., 2020; Krolewiecki, et al., 2020; Elgazzar, et al., 2020; Chaccour, et al., 2021; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

A single-center prospective clinical trial performed in 167 patients with mild to severe COVID- 19 from Argentina, found that none of the mild or moderate cases of COVID-19 who received the experimental treatment with Ivermectin were hospitalized, and only one patient died (0.59%) (Carvallo, et al., 2020; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv). In México a comparative effectiveness study was performed among patients with laboratory-confirmed SARS-CoV-2 infection. The experimental group received a TNR4. TNR4 consists of four drugs administered orally to COVID-19 cases with mild or moderate symptoms: (1) Ivermectin, 12 MG single dose; (2) azithromycin 500 mg for 4 days;

(3) montelukast, 60 mg on the first day and then 10 mg between days 2 to 21; and (4) acetylsalicylic acid, 100 mg for 30 days. This study indicated that the TNR4 significantly increases the likelihood of full recovery within 14 days after the onset of symptoms, and decreases the risk of hospitalization or death among ambulatory cases of COVID-19 (Lima-Morales, et al., 2021; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

The addition of Ivermectin to standard care can be effective for the treatment of COVID-19 patients with significant reductions in mortality and duration hospital stay compared to Hydroxychloroquine plus standard treatment (Elgazzar, et al., 2020). Early use of Ivermectin is very useful for controlling COVID-19 infections, improving cytokines storm and prophylaxis of frontline health care as well as household contacts (Elgazzar, et al., 2020; Chahla et al., 2021 preprint Research Square; Chahla et al., 2021 preprint medRxiv).

The controversial findings around the efficacy of Ivermectin in COVID-19 is currently preventing from making firm recommendations to clinicians. Metaanalyses that included studies with a variety of regimens have reached different interpretations and conclusions, preventing the achievement of consistent findings (Padhi, et al., 2021; Bryant, et al., 2021; Roman, et al., 2021; Neil, et al., 2021). In view of this situation, the Ministry of Health of the Province considered a MEURI Program as a resource to attempt the monitored and controlled use of a treatment not approved for this indication but with preliminary results of adequate safety and potential efficacy. A recent work carried out by the Ministry of Health of La Pampa, Argentina (Mayer, et al., 2022) on a MEURI Program of high-dose Ivermectin in COVID-19 patients highlights the safety and possible efficacy of this drug for the management of COVID-19 patients.

Although our study has some limitations such as the low number of patients who were included, however, it is representative for the number of primary health care centers belonging to the Public Health Systems of Tucumán, Argentina. It's a descriptive study of clinical follow-up at 28 days without report of adverse events which it would be beneficial to evaluate in future works. Or study demonstrates similar benefits with other studies, and taken together, these results are encouraging for further study about repurposing Ivermectin for the treatment of COVID-19, considering that it is an inexpensive drug and is accessible in the local pharmaceutical industry (Argentina). We suggest new clinical intervention studies in our region and other countries that may show the effect of the IVER compound in mild-stage outpatients.

5. Conclusion

This work supports the potential efficacy of Ivermectin in outpatient care with mild COVID-19 as a potentially useful intervention of public health consideration. When considering our results in the context of other clinical studies evaluating the use of Ivermectin in the treatment of patients with COVID-19, we can conclude the potential clinical utility of this drug in population groups of patients with mild COVID-19 disease. This study highlights that IVM is an intervention that warrants careful, public health-based consideration for the treatment of patients during with COVID-19 until superior and affordable therapeutic alternatives become available.

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Declarations

Ethics approval and consent to participate

The people who agreed to participate in the study gave their informed consent before starting the study. The protocol was approved by Independent Ethical Committee / Health Research Directorate, Ministry of Health, Tucumán Government, Argentina, IRB: 054/2020 in accordance with the ReNIS, National Register in Health Research, Argentina /0032.

Consent for publication

"Not applicable"

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The database collected for the study will be made available on request for scientific interests. Information available includes: investigation protocol, informed consent and database of trial with ID numbers to protect patient´s identity.

Conflict of Interests

The authors did not receive any monetary compensation for this work. They declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The Ministry of Public Health. Tucumán, Argentina participated in the design of the study and the collection, analysis and interpretation of the data, as well as in the drafting of the manuscript.

Authors' contributions

ESO supervised the database. GGB, ESO and DGG contributed with the data processing and contributed to the statistical analysis. ESO, DGG and MPB were responsible for writing the manuscript. TM, YB and PT contributed to data collection. REC and LMR were the institutional managers to carry out the work. MPB supervised the project.

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