MEXICAN SOCIAL SECURITY INSTITUTE

FAMILY MEDICINE UNIT No. 20 VALLEJO

1. TITLE OF THE INVESTIGATION PROTOCOL

"PRONOSTIC MODIFICATION IN PATIENTS WITH COVID-19 UNDER EARLY INTERVENTION TREATMENT IN U.M.F 13 AND U.M.F 20".

IDENTIFIERS: NCT04673214

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2. SUMMARY

“EVALUATION OF PROGNOSTIC MODIFICATION IN COVID-19 PATIENTS IN EARLY INTERVENTION TREATMENT”.

Introduction: Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potential fatal disease generating a global public health problem. Person-to-person transmission of COVID-19 infection led to the isolation of patients who subsequently received a variety of treatments. Ivermectin treatment in relation to its safety is approved for human use by the FDA in parasitic and skin infections. Studies report the therapeutic safety of Ivermectin in humans with COVID-19, describing a 6.1-fold decrease in lethality compared to patients who did not use Ivermectin (1.4 vs. 8.5%, p <0.0001). In this sense, the WHO and PAHO encourage the use of unproven therapies in the context of a randomized clinical trial (RCT). Anticoagulants have reported up to 20% in the reduction of mortality (heparin), Ribaroxaban is effective with the inhibition of PAR1 / PAR2 / PAR4 receptors through the blocking of Factor Xa and the formation of thrombin, having anti-inflammatory effects, decreasing arteriosclerosis and platelet aggregation. There is a Telemedicine working method implemented by the OOAD of the Northern Federal District, which detects early signs and symptoms of possible complications and offers an early intervention treatment policy for first-level care beneficiaries. Under this method, a quasi-experimental study that shows that there is a modification in the frequency of recovered patients of 80 -90% in patients diagnosed with COVID-19 after an early intervention treatment with paracetamol, Ivermectin, Azithromycin, Ribaroxaban in patients with COVID -19 from UMF 13 during the period of July-August 2020. Therefore, it is necessary to carry out a randomized clinical trial to confirm this assertion.

Objective: To evaluate the percentage of patients with a diagnosis of COVID-19 who modify their clinical evolution under a comparative treatment of early intervention in beneficiaries of the U.M.F 13 and U.M.F 20 of the I.M.S.S., during the period of December 2020- February 2021.

Material and Methods: A randomized, single-blind, prospective, longitudinal and open experimental study in 62 patients with COVID-19 from UMF No. 13 and No. 20 from November to December 2020. Including 31 patients in group A (Azithromycin / Ivermectin / Ribaroxaban / Paracetamol) and 31 patients in group B (Azithromycin / Ribaroxaban / Paracetamol). With inclusion criteria over 18 years of age, have type 2 diabetes mellitus, Systemic Arterial Hypertension, Obesity or overweight, PCR confirmation of COVID-19. For

the video call, the Family Medicine Units have Installation of Electronic Equipment for Internet use. Exclusion criteria are patients with severe COVID-19 (they deserve immediate referral to second level of care, hospital). Elimination criteria are Prior informed consent, medication is given randomly to a COVID-19 patient, a follow-up video call will be made at home for 14 days, recording sex, age, schooling, date of disease onset, taking laboratories (hematic biometry, C-reactive protein, D-dimer, Ferritin, prothrombin time, thromboplastin time, lactic dehydrogenase) taken at the onset of the disease, taking as an outcome variable the modification of the clinical course (clinical symptoms such as headache, cough, fever, conjunctivitis , myalgia, arthralgia, rhinorrhea, odynophagia, anosmia, chest pain, dyspnea) when giving treatment in groups A and B.. Statistical differences will be evaluated using Pearson's Chi-square test or Fisher's exact test, with a power of 90% and a type I error rate of 1% for the variable of modification of the clinical evolution in the groups of treatment A and B. The analyzes will be carried out in SPSS version 21. It is a feasible study since it has the infrastructure and supplies as well as the experience of the researchers for the management of COVID-19 patients, being an associate researcher Hematologist to contribute his experience in the surveillance of these patients. Estimated time for completion: December 2020- February 2021.

Keywords: COVID-19; outpatient follow-up telemedicine; early intervention treatment.

3. Theoretical Framework

In December 2019, the World Health Organization (WHO)was reported to detect pneumoniaof unknown causes in Wuhan Province, China. On 13 January 2020, Thailand's Ministry of Public Health reported the first imported case of the new laboratory-confirmed coronavirus 2019-nCov, the first case being confirmed outside China. This outbreak was declared on January 30, 2020 as a public healthemergency of internationalinterest. On 11 February 2020, WHO announced the name for the disease caused by the new coronavirus: COVID-19. On the same day, the International Committee on Virus Taxonomy announced SARS-CoV-2 as the name of the nuevo virus that causes COVID-19. On 11 March 2020, WHO reportedCOVID-19 as a pandemic. By March 13, 2020,the s 5,000 deaths had already been achieved for this cause, and Europe was subsequently the epicenter of a greater number of cases and deaths than the rest of the world, not counting China. [1]

On February 26, the first case of coronavirus was reported in Latin America, specifically in Sao Paulo, confirmed by the Brazilian Ministry of Health as a male with a history of travel to Lombardy, Italy. On February 28, the first case was confirmed in Mexico City, in a 35-year-old male who also had a history of traveling to Italy. [2]

With respect to the Americas region,the United States of America contributes the majority ofcases and deaths (89% and 90% respectively), distributed in all 50 states. In North America, a4.75% chance of lethality is reported. [3]

4.1 Epidemiology

At the beginning of May, there were 1,035,353 positive patients with Covid-19 in the United States of America; value that doubled in less than two months. And as of October 22, 2020, this count amounted to 8,184,788; which translates as a 690% increase in cases compared to the existing ones at the beginning of May. WHO currently estimates that around 60,155 new cases confirmed with Covid-19 occur each day in thiscountry. [4]

Similarly, the exponential increase in mortality was also reflected by the number of 62,637 deaths at the start of May and from 219,497 to 22 October; suggesting that on average, 896 people died each day from Covid-19 in less than six months. [4]

These epidemiological figures contrast significantly with those of the People's Republic of China, where active cases declined significantly from the second half of February. So from May (at which point 84,391 patients were infected) to October 2020, only 7,197 new confirmed cases positive for the virus were reported, an average of 23 to 41 per day. It should be noted that the relationship between the incidence of cases and deaths has

also been proportional. In less than six months, only 103 patients have died of Covid-19, which would be assessed as 0.58% of deaths per day as of May [4]

According to WHO, the median age in China was 51 years, with most cases between the ages of 30 and 69. Regarding sex there is a slight predominance of the male sex with 51%. [5]

As of May 06, 2020, 3, 588,773 confirmed cases and 247,503 deaths have been reported worldwide. The overall fatality rate is 6.9%. In Mexico, 27,634 confirmed cases, 17,553 suspected cases and 2,704 deaths have been reported. [6]

Men have been slightly more affected by 58.48% compared to women with 41.52%. 59.34% of patients have received outpatient treatment, while 40.66% have required hospitalization. [7]

Speaking specifically of Mexico, according to data obtained by the Ministry of Health, the percentage of confirmed patients positive with SARS-CoV-2, has grown alarmingly as of May 2020. At the beginning of that month, the number of infected was limited to 23,471 patients. From that time until the beginning of August, the figures released to 456,100 active cases. [8]

During the month of August, a second spike in contagion gradually resulted. With this, 847,108 accumulated active cases have been reached until 17 October; equivalent to approximately 4,706.5 new infected patients per day in less than six months. In this regard, and exclusively throughout October, 748,315 cumulative confirmed cases had been identified at the beginning of the month; as of October 17, it was possible to count 847,108 sick patients, with a 13% increase between the first and second figures so far this month. [8]

As for the suspected cases, a stable number of patients are reported, with a sudden and only significant increase at the end of September, maintaining from there, a new and relative stability. Thus, the number of suspected patients accumulated amounts to 316,228 cases.

The mortality curve also had unsettling growth from late April to mid-May. In the latter, a number of 5,177 deaths were conceptualized; however, this amount multiplied to the extent of reaching 86,069 deaths, with an average of 462 deaths per day in the last 6 months. [8]

In summary, as of October 17, 2020, there are a cumulative total of 847,108 confirmed patients, 316,228 suspected cases and 86,069 deaths in ourcountry. [8]

The median incubation period is 5-6 days with a range of 1 to 14 days. [9]

Transmission is considered to begin 1 to 2 days prior to the onset of symptoms, although it is still unknown whether from symptomatic people the intensity of transmission is the same as in asymptomatic people. It has been noted that most infected patients have a high viral load (up to 104 and 108 copies of genome/ml per nasopharyngeal or saliva sample) as measured by RT-PCR. However, patients with mild infection, the peak viral load occurs during the first 5-6 days after the onset of symptoms and practically disappears on day 10. Although post-day 10 viruses are detected in some patients, the viral load is 100-1,000 times lower, so low transmission capacity is expected these days. In addition, with viral loads below 105 copies there is no growth of the virus in crops. This suggests that, in people with mild symptoms, chance of transmitting the infection to others would be very low after the first week after the onset of symptoms, even when the virus is still detectable by PCR. In people with severe infection the viral load is up to 60 times higher than those of milder course and viral excretion may be more durable. [5]

The average time between onset of symptoms and recovery in patients with mild illness is approximately 2 weeks and in patients with severe or critical disease is 3 to 6 weeks. Preliminary data suggest that the time it takes for the severe disease to develop is 1 week. The time between onset of symptoms and death is between 2 and 8 weeks. [5]

The R0 (basic number of reproduction) in the first months of the epidemic in Wuhan China was estimated to be between 2 and 3, subsequently in study reviews this value is estimated to be between 1.5 and 6.5. It should be noted that the public health and social estating measures imposed have had an impact on the decrease in this number. Accurate estimate of lethality during an outbreak is complicated as cases are updated daily and adjusted. The use of models has estimated lethality between hospitalized cases 14% (IC95%), and in the general population between 0.3 and 1%. [5]

4. 2 Structure

The viral particle has a diameter of 60 x 100 nm and appears round or oval. It belongs to the group of viruses involved. It has a single-category RNA genome with a positive, non-segmented sense of 29.9Kb.

Similar to another β- CoVs, SARS-CoV-2 virion has a nucleocápside composed of genomic RNA and phosphorylated nucleocapsid protein (N). The nucleocápside is covered by a phospholipid bipa, which in turn has 2 different types of peak proteins: peak

glycoprotein (S), triteric, which exists in all CoVs, and hemaglutinin-esterasse (HE) only shared among some CoVs. Membrane protein (M) and wrapping protein (E) are among the S proteins in the viral envelope. The SARS-CoV-2 genome has terminal sequences of 5o and 3o (265 nt on the 5 terminals and 229 nt on the 3 terminal), which is typical of β-CoVs. SarS-CoV-2 predicted genes S, ORF3a, E, M and N are 3822, 828, 228, 669, and 1260 nt in length, respectively.

Similar to SARS-CoV, SARS-CoV-2 carries a predicted ORF8 gene (366 nt in length) located between the M and N ORF genes. [10]

4.3 Physiopathology

4.3.1 SARS-CoV-2 invasion mechanism in host cells

SARS-CoV-2 penetrates the cell using angiotensin-converting enzyme 2 (ACE-2), a membrane exopeptidase present primarily in the kidney, lungs and heart as a receptor. The function of ACE2 is the transformation of Angiotensin I into Angiotensin 1-9 and Angiotensine II in Angiotensin 1-7. These end products have vasodilator, antifibrosis, anti-inflammatory effects and promote natriuresis. They are all effects, therefore, that reduce blood pressure, counterregulating the action of Angiotensin II. ACE2 has been linked to protection against hypertension, arteriosclerosis and other vascular and pulmonary processes. In animal models it has been seen that the absence of ACE2 results in increased lung damage in the SDRA and the overexpression of ACE2 protects against it. In contrast, the angiotensin-converting enzyme (ACE), which transforms Angiotensin I into Angiotensin II, promotes the generation of secondary peptides with vasoconstrictor, pro-inflammatory and sodium retention effect, which are related to the physiopathology of high blood pressure. Severe cases of COVID-19 have been observed to have very high levels of Angiotensin II. And the level of Angiotensin II has been correlated with SARS-CoV-2 viral load and lung damage. This imbalance of the renin-angiotensin-aldosterone system could be related to the virus's inhibition of ACE2. This same effect was already observed in the SARS outbreak in 2003. [11]

4.4 Clinical picture

The route of transmission between humans is through the secretions of infected people, mainly by respiratory droplets of more than 5 microns[10,11,]which are able to reach up to 2 metros away, reaching theSARS-Cov-2in objectas copper, chore, stainless steel and plastic surfaces,shown to last4, 24, 48 and 72 hrs when maintained at 21-23oC and with 40% humidity. On paper it is no longer detected after 3 hrs, wood, ropa or glass up to 1 to 2 days, > 4 days in stainless steel, plastic, money banknotes and surgical masks. [12]

A three-countryr eporte is present with the following symptoms and signs in sarS-Cov-2 patients:

Fever(87%)[12]	Fever(68.7%)[12]	Fever[13]
Dry cough (67.7%)	Those (68.1%)	Dry cough
Asthenia (31%)	Dyspnoea (31%)	Headache
Expectoration (33.4%)	Chills (27%)	Dyspnea
Dyspnoea (18.6%)	Sore throat (24.1%)	Myalgias or Arthralgias
Sore throat (13.9%)	Diarrhea (14%)	Anorexia (SD)
Headache (13.6%)	Vomiting (6%)	Dizziness (SD)
Myalgias or arthralgias (14.8%)		Runny nose
Chills (11.4%)		Conjunctivitis
Nausea or vomiting (5%)		Chest Pain
Nasal congestion (4.8%)		
Diarrhea (3.7%)		

Hemoptisis (0.9%)		
Conjunctival congestion (0.8%)		
In China with 55,924 cases	**Spain with 14,011 cases**	**Mexico with 29,616 cases**

SD: No data

The incubation period is 5-6 days, with a range of 1 to 14 days. 97% of symptomatic cases develop within 11.5 days after exposure. [12]

Clinical manifestations are not yet clear, as reported symptoms vary are usually mild and begin gradually, although severe intakes(dyspnoea, pneumonia) mayoccur. [14] The most reported symptoms in Mexico are fever, dry cough and headache. [13] Wuhan also reported other symptoms related toorgans and systems[12]:

Cardiac	The disease can occur with related symptoms of heart failure or acute myocardial damage, even in the absence of fever and respiratory symptoms. [12]
Neurological	Wuhan reported study with 214 patients of whom 36% had neurological symptoms: Dizziness (17%), Consciousness disturbances (7%), Stroke (2.8%), Vascular brain accidents (2.8%), ataxia (0.5%)
Otorrinolaringológicos	The most common reported: facial pain, nasal obstruction, anosmia- hyposmia, dysgeusia-hypogeusia.
Hematologic	Thrombotic phenomena associated with COVID-19 cases that manifest as stroke, cardiac ischemia, sudden death, embolism, TVP*

*TVP (Deep Vein Thrombosis).

Source: prepared by Scientific-Technical Information. Coronavirus Disease, COVID-19[12]

It has now been reported that most hospitalized patients have some comobility; high blood pressure and diabetes are the most common. [14] Other comorities, lung problems, cancer, immunocompromised people are more likely to have severe pictures.

Increased D-dime and to a lesser extent increased prothrombin time and thrombocytopenia have been considered markers of poorer severity and mortality prognosis. [14]

Symptomatology presented in patients with COVID-19 has shown that real-time polymerase chain reaction (RT-qPCR) is the most efficient for diagnosis [15]

4.5 Covid-19 diagnosis

Clinical diagnosis of COVID-19 is based primarily on epidemiological history, clinical manifestations and other auxiliary studies, such as nucleic acid detection, computed tomography, IgM/IgG immune identification technology, ELISA and blood culture. [15]

Clinical signs and symptoms of SARS-Cov2-infected patients are atypical, including respiratory symptoms such as cough, fever, dyspnoea, andpneumoní to viral. Therefore, auxiliary studies are necessary for confirmation ofinfection with thisvirus. [15]

4.6 Nucleic acid detection technology

The two most commonly used studies of this type are real-time polymerase chain reaction (RT-qPCR) and high-performance sequency. The authorized methods for detecting the virus is high-performance sequencing and blood virus culture, but the application of the first method depends on very high-cost equipment, so RT-qPCR is the most common, effective and simple for secretion virusdetectionis respiratory and blood. [15]

Taking into account symptomatology and laboratory studies for their diagnostica confirmation in patients withCOVID-19,se have developed technologies of information and communication (ICTs) to perform clinical follow-up inpatients with cardiovascular diseases and in older adults who have succeeded such as the Monitoreo of patients at home, Remote Monitoring and Telemedicine/Telehealth.

3.9 Information and Communication Technologies (TICs)

Information and Communication Technologies (ICTs)form the set of resources necessary to manipulate information and particularly the computers, software and networks necessary to convert, store, manage, transmit and find it. They are also used as means of learning aid and represent a basic competence that must be disseminated regardless of the age of individuals, they offer us great opportunities for all groups of society, regardless of how old they are, but it is necessary to know the needs, interests, concerns and possible limitations of all citizens to bring them closer to them. [16]

As Sampadarefers, in his review paper information technologies "has the potential to improve the quality, safety and efficiency of health care". So medical staff, nursesenter others can access and use the correct information that the patient needs. [17]

Se has suggested that older adults must take on this change and adapt to these new forms of communication; otherwise they will be people who will gradually become ingested, which can negatively affect their health, since the use of technology is related to a lower manifestation of problems associated with mental health and a higher rate of integration and participation. [18]

Educational programmes for Older Adults (AM) include, among other possibilities, the approach of the AM to ICTS, presenting these great interests, given the importance of them today and their relevant role, not only as content, but as a means of providing other training to recipients. [19]

3.9.1 Monitoring patients at home.

Sampada says that due to staggered health costs in health care, home monitoring may be applied particularly in older adult patients with chronic illness. Information has been recorded of patients with cardiovascular problems through phone calls, making it easier for the doctor to use this tool. [17]

3.9.2 Remote monitoring

Remote monitoring is the electronic transmissionof health care dataentered directly by a patient (or theircare provider) or through a physician to an Electronic Health Registration (EHR) deviceor the Personal Health Register of the patient(PHR). A clinician's

ability to monitorpatient information duringdiagnosis, drug tracking and daily life activities(ADL) measurements, captured remotely, is a key enabler for the managementof chronic health problems and management ofnuevas conditions. Remote monitoring may include physical measurements (e.g. weight, blood pressure, heartrate, pulse oximetry, gucosa), diagnostic measures, drug tracking, device information(e.g. pumping drugs,infusion devices, electronic pillboxes) and daily life measurement activities (e.g.ADL biosensors, pedometers, sleep activity, etc.) . [17]

4.9.3 Telemedicine/Telehealth

Telemedicine is the use of telecommunication technologies to provide health and information-related servicesthat support care for thecountry, administrative activities, health education, health services and general health information. It is a new method of health care that shares and/or exchanges patient-related data and medical opinion between amedical speculator and a doctor in a remote location through telecommunication networks. Technology is a means to improve access to care, whilereducing the cost of transportation and increasing the convenience of patient care. Television - omiciliary care, videoconferencing and electronic health records are all components of Tele health and use of information technology to provide a service. [17]

Karen Donelan's reports in a transversal study, where 254 people visited by Telemedicine were found for 15 minutes, reported in herpatient experience with virtual video visitsby three different specialists (psychiatrist, neurologist, cardiologist) answers > 90% with "if, definitely agree"rating, questions focused on whetherthings were explained inaneasy way to understand, whetherthe patient's care would be heard and whether he feltthat the doctor had spent enough time on the patient when performing the video call. [20]

With the presence of COVID-19 in Mexico City at the Mexican Institute of Social Security, a follow-up tool is developed through the Tecologies of lto Information and Communication (TICs),as sonthe video calls with the aim of giving follow-up to signs and symptomsof COVID-19 and offer an early intervention treatment policy according to THE IMSS COVID-19 patient management scenarios,this is called the Outpatient Monitoring Model.

4.8 MOutpatient Tracking Odelo

An Outpatient Monitoring Model means a process that during Phase 3 contingency in patients with COVID-19 rightholders of the IMSS is granted by the Unconcentrated Administrative Operation Body of the Northern Federal District, to follow up on patients diagnosed clinically, confirmed and graduated from COVID-19 in righthabientis first levelof care that within the specific objectives is to detect early signs andsymptoms of possible complications, andvalue the status of the patient's(possible) co-ntactos,to sesorar al paciente ifnecessary,or torgar follow-up appointment in the Unit for revaluation, to offer an early intervention treatment policy according to THE IMSS COVID-19 patient management scenarios , that the drugs be counted according to the availability of the unit, in top-level rightholders. A flowchartis developed to track patients suspected of COVID-19, in which COVID-19 (Respiratory Module) patient care facilities are considered, which counts the first-level units of care, as well as the staff involved in the management of the patient in the respiratory module such as the nurse, the laboratorist, the family doctor and cleaning and hygiene personnel, which in turn coordinates with Staff of Heads of Service, the area of performance control, nursing and clinical coordination of health education and research, this in order to integrate a means of monitoring through the Information and Communication Tecologies (TICs),such as phone calls or video calls with the use of computer equipment, database, telephone line and internet, necessary to comply with the monitoring of the model. (See Table 2, 3 Y 4) . [21]

In relation to the Monitoring of patients with Clinical Phase Leve Covid-19 in the First Level Of Care Units of the Northern Delegation, they will be carried out in the triage modules, which initiates medical care when the patient is taken vital signs by nursing personnel and questioned about alarm data (dyspnoea, chest pain); in case of presenting alarm data you are given a reference to second level of attention. If you do not present alarm data, you enter a doctor's office and question compliance with the operational definition for COVID-19, the presence of three major symptoms such as headache, cough or fever, and at least one of the following minor symptoms such as conjunctivitis, myalgias, arthralgias, rhinorrhea, odinophagia, anosmia, chest pain, dyspnoea; when complying with the operational definition for COVID-19 the patient will be shown COVID-19 confirmatory PCR, if the test is positive the patient is informed about the early intervention treatment provided, informing you through informed consent with the specifications set out therein (see Annex 1) and also informing the patient that they must have a smartphone (with installation of the WhatsApp application) for making video calls. If the patient agrees to sign the informed consent, he or she is given a COVID-19 Information Triptych, the pharmacological medicinal product is delivered, upon randomization (see Table 4), and is indicated to follow up by video calls that were performed over 14 days, lasting

approximately 15 minutes each video call, with the monitoring and recording of clinical symptoms, adverse reactions to the medicines administered and alarm data if sent to a second level of care. (See Table 1)

Table 1. Monitoring patients with Covid-19 Mild Clinical Phase in the North Delegation's First Level of Care Unit

Triage staff (1 nurses)

Rightholders with Respiratory Symptoms

Filter staff

Taking vital signs

Do you present alarm data?

No

Go into the doctor's office

1 doctor

Interrogation aimed at COVID-19 symptoms

Does not meet operational definition

Treat pathology

Yes meets operational definition

1 laboratorist

Enter respiratory module

Yes

Second-level reference

Tracking

Daily video call for 14 days (recommendation takes rest and movement oxymetry)

1. **Give triptychs of information**
2. **Give symptomatic treatment**
3. **Explain tracking through video calls for 14 days**
4. **Isolation at home for 14 days**

Accepts

Go to office

-Screening 1 in 10

(COVID-19 confirmatory PCR

Applicatio n of tests, symptoms and signs

Pharmacological intervention by the doctor confirmed by PCR test

Information about symptoms and warning signs for second-level care reference.

Send to Second Level immediately.

Give symptomatic treatment, explain alarm and isolation data at home for 14 days

Doesn't accept

Write down Phone Number on informed consent and

Ye s

It has cell phone equipment the patient or primary caregiver

No

Not compliant for video calling tracking

Table 2. PERSONNEL INVOLVED IN THE USE OF ICTS	
PERSONAL	**FUNCTIONS**
CLINICAL COORDINATOR OF HEALTH EDUCATION AND RESEARCH	Coordinate and monitor monitoring of COVID-19 patients
HEAD OF SERVICE	Conduct the census of the cases to be followed and will ask the area of benefits for patient data (No. Telephone) and designate the staff to carry out or who will develop the follow-up
PERFORMANCE CONTROL	It will provide the information required by the head of department
FAMILY DOCTOR AND/OR SOCIAL SERVICE MEDICINE INTERN	You will make follow-up calls and make a record of it in the census made

Table 3. MATERIAL USED	
COMPUTER TEAM	TELEPHONE LINE
DATABASE	INTERNET
TELEPHONE LINE	TRIPTYCHS AND TESTS

Table 4. Earlyintervention treatment policy medications in COVID-19 patients

Medication	**Dose**	**Range**	**DURATION (DAYS)**
PARACETAMOL 500 mg TAB	500 MG VIA ORAL	EVERY 8 HRS IN CASE OF FEVER > 38th C	3 DAYS
AZITROMICINA 500 mg TAB	500 MG VIA ORAL 250 MG VIA ORAL	EVERY 24 HRS EVERY 24 HRS	FIRST DAY SECOND TO FOURTH DAY
IVERMECTINA 6 MG TAB	2 TABLETS < 80 KG VIA ORAL 3 TABLETS between 80-110 kg VIA ORAL 4 TABLETS > 110kg VIA ORAL	EVERY 24 HRS	2 DAYS
RIVAROXABAN 10MG	1 TABLETA VIA ORAL	EVERY 24 HRS	10 DAYS

In relation toearly interventional treatment policymedications in COVID-19patients, Ivermectin, Azithromycin, Rivaroxaban and Paracetamol are considered as part of the monitoring of patients with clinical phase leveCovid-19in the Unitsis of first level of care of the Northern Delegation.

4.7 Early Intervention Treatment Policy Drugs in COVID-19 Patients

4.7.1 Ivermectin

Ivermectin is an FDA-approved broad-spectrum antiparasitic. It is usually administered with a single dose of 150 µg/kg orally. Ivermectin has been shown to stimulate human immunity (including the production of IL-1 and other cytokines, activation of superoxide anion production and increased lymphocyte response). [22]

Several studies report antiviral effects of Ivermectin on RNA viruses such as Zika, Dengue, Yellow Iebre F,WestNile, Hendra, Newcastle, Venezuelan Equine Encephalitis, Chikungunya, Semliki Forest, Sindbis, Avian Influenza A, Human Immunodeficiency Virus Type 1 and Severe Acute Respiratory Syndrome coronavirus 2. [23]

Mechanism ofaction, absorption and distribution.

In vitro studies have shown that Ivermectin has antiviral effect such as that performed by Arshad U. et to where it refers in in vitro studies a response to SARS-COV-2 infection where Ivermectina has a maximumsimulated plasma concentration of lung (Cmax) / maximum mean effective concentration (CE50) above 1, which means having pulmonary concentrations above your CE50 more than 10 times and in lung tissue has a value of 20.01(Cmax)/ (CE50) and means presenting lung concentrations above your CE50 by more than 10 times. [24] Similarly, that performed by Caly L, et al. recently showed that a single dose treatment with Ivermectin induced a reduction of approximately 5000 times in the viral RNA of SARS-CoV-2 at 48 hrs in a cell culture model Vero-hSLAM. Mentioning that Ivermectin is not if handled at a standard dose, making it a strong candidate for evaluation in clinicaltrials. [22.]

In addition, no toxicity of the drug has been seen. Ivermectin is known to inhibit the nuclear amount of viral and host proteins. Virus integrase protein and importin (IMP) α/β I

is responsible for the nuclear amount which increases infection. Because most viruses are dependent on IMP α/β I, Ivermectin inhibits the amount andinhibits viral replication. [25]

Within the pharmacokinetic action of absorption and elimination of Ivermectin as possible treatment of COVID-19 stands out what is mentioned by Momekov G. et al. with pharmacokinetic absorption parameters of 20.2 - 38.2 C max (ng/mL) and elimination parameters of 3.1 - 7.57 Cl (1 $kgx^{1}day^{x\ 1}$) at a dose of6mg of Ivermectin, considering the expectation of reliable data from controlled studies. [26]

Therapeutic uses and dosages

A conventional dose (200≤ g/kg) of Ivermectin is recommended asa safe regimen in human therapy. [23]

Use of Ivermectin in COVID-19

Randomized Clinical Trials(ECA) that have used Ivermectin as a treatment for COVID-19 patients have been conducted, however some studies are still in the recruitment phase. [27] WHO and PAHO encourage the use of unproven therapies in the context of a randomized clinical trial (ECA). [28]

A study conducted by Drosedal S. et. al. refers to the fact that clinical efficacy of Ivermectin has been established in combination with hydroxychloroquine. [29] The randomized clinical trial (Phase 1 pilot study) conducted by Gorial F. et al. where they evaluate the effectiveness of Ivermectin as treatment en patientsCOVID-19 , with criterios of inclusion in over 18 years of age, diagnosis with positive polymerase chain reaction test (PCR) <3 days and hospital admission to the Al-Shifa'a Hospital Center, initial results are reported in 16 patients with treatment based on Ivermectin 0.2mg/kg single dose, Hydroxychloroquine 400mg on the first day and then 200mg orally for 5 days, Azithromycin 500 mg during the first day and then 250mg for 5 days, 4-week follow-up, with initial referred results of average age 44.8 years (±10.6), male sex 68% (n-11), mild symptoms 56.3% (n-9), moderate symptoms 43.8 (n-7), predominantly cough 81.3% (n-13) and fever 68.8% (n-11), with presencia de comorbilidades (diabetes mellitus e hipertensión arterial en 3 pacientes, (NCT04343092, US National Library of Medicine, 2020). [30]

There is a case-series study, prepared by Aguirre-ChangG. demonstrating an Ivermectin treatment scheme for patients with COVID-19, with 6 mg tablets; with adult doses of 2 tablets per day for 2 days, weighing between 80 and 100 kg; give 3 tablets a day and > 110 kg; give 4 tablets a day for 2 days, without reports of risks during use in this dose. Considering initiating therapeutics in COVID-19 patients with mild symptomatology (mild severity), during the onset days of symptoms 1 to 5 days of COVID-19, in home isolation with health care. [31]

Given these results from clinical trial studies using Ivermectin,further evidence isstill needed for the treatment of COVID-19 infection,as referred to in Lespine A. et al. considering the need for more research to better evaluate the effectiveness of Ivermectin for the treatment of respiratory viruses such as SARS-CoV-2. [32]

4.7.2 Azithromycin

Azithromycin is a drug in the macrolide family. Macrolides and cetolides are effective in treating respiratory infections caused by common pathogens of community-acquired pneumonia. Except for Azithromycin,all have important pharmacological interactions by inhibitinghepatic CYPenzymes. [33]

Mechanism of action

This type of antibiotics are bacteriostatic that inhibit protein synthesis by reversible binding with the 50S ribosome subunits of sensitive microorganisms, at or very close to the site for chloanphenicol binding. [33]

Research shows that Azithromycin acts as a weak lipophilic acidotrophic base which modulates the pH of the endosomas and Golgi apparatus. This leads to in vitro effects onintracellularorganelos similar to the conferidos effects by hydroxychloroquine. [25]

Antimicrobial activity

Azithromycin has appropriate activity against Moraxella catarrhalis, Chlamydia spp, L. pneumophila, B. burgdorferi, M. pneumoniae and H. pylori. It has intense activity against Mycobacterium avium-intracellulare, itself as against some protozoars, such as Toxoplasma gondi,Cryptosporidium and Plasmodium spp. [33]

Absorption

Oral Azithromycin is rapidly absorbed and distributed throughout the body, except for the brain and CSF. It should not be administered with food. It can also be administered intravenously, resulting in plasma concentrations of 3 to 4 mcg/ml after an infusion of 500 mg per 1 hour. [33]

Distribution

Azithromycin has extensive tissue distribution and high concentrations in cells (including phagocytes), resulting in much higher concentrations in tissues or secretions, compared to simultaneousserum concentrations. [33]

Elimination

Azithromycin undergoes some liver metabolism to disable metabolites, but biliary excretion isthe mainroute of elimination. Only 12% of the drug is eliminated without changes in urine. The average elimination time is 40 to 68hours and lasts because the tissueuptake and binding are extensive. [33]

Therapeutic uses and dosages

Azithromycin should be given 1 hour before or 2 hours after meals when administered orally. For outpatient treatment of community-acquired pneumonia, pharyngitis or skin infections, an impregnation dose of 500 mg is used on the first day and then prescribed 250 mg daily for days 2 to 5. Azithromycin is an appropriate treatment for community-acquired pneumonia, in hospitalized patients it is often added to a cephalosporin to coveratypical respiratory pates. [33]

Side effects

Macrolide antibiotics cause QT prolongation by an effect on potassium ion ducts. Therefore, Azithromycin may be associated with a small increase in the risk of cardiac death. [33]

Mechanism of action of Azithromycin in COVID-19

Azithromycin has in vitro effects on COVID-19 as Choudhary R. et al refers in its in vitro study on intracellular organelles with COVID-19 infection, Azithromycin acts as a weak lipophilic acidotrophic base that modulates the pH of endosomas and the network Golgi's device. [25] Other authors have referred to other mechanisms of action of COVID-19, as referred to by Sargiacomo C. et. al. questioning that a treatment to prevent Coronavirus infection such as Azithromycin that acts functionally as an anti-inflammatory drug and reduces senescence-associated secretory phenotype (SASP) mediators, such as IL-1beta and IL-6; in addition to Azithromycin also inhibiting replication of other viruses, such as Zika and Ebola. [34] Rahman MT. refers that Azithromycin inhibits viral replication and IL-6 production, IL-1 or IL-1R, suggesting this drug for the prevention and treatment of COVID-19 disease. [35] Dos Santos WG.et the. refers to the in vitro concentration EC50 (effective concentration of 50%) for Azithromycin against SARS-CoV-2 was determined as 2.12 M after a subsequent incubation period of 72 h of infection. It also refers to the that most cytokines induced by Azithromycin are related to the response to viral infection and, in turn, induce resistance to viral replication in target cells. [36] In vitro Azithromycin is approved by the FDA (U.S. Food and Drug Administration) because it reveals its potential inhibition of SARS-CoV-2 replication. [37]

Absorption and distribution of Azithromycin in COVID-19

Within the pharmacokinetic action of absorption and distribution of Azithromycin as possible treatment of COVID-19 stands out the referred by Arshad U. et to which Azithromycin has a maximum simulated plasma concentration of lung (Cmax) / maximum mean effective concentration (CE50) above 1, which means presenting lung concentrations above your CE50 more than 10 times and in lung tissue has a value of 16.04(Cmax)/ (CE50) and means presenting lung concentrations above your CE50 by more than 10 times. [24]

Use of Azithromycin in COVID-19

Randomized clinical trials that have used Azithromycin as a treatment for COVID-19 patients have been conducted as Gautret P, et al. 36 COVID-19 patients, forming three groups, group 1 (control) of 17 patients, group 2 (HQN monotherapy) of 19 patients and group 3 (AZT and HQN) of 11patients, with the aim of describing the results of the negative

NASopharyngeal PCR virology test up to 6 days of follow-up, with a result of On day 4, 83% of patients treated with hydroxychlorokine

and Azithromycin were virologically cured, compared to 50% patients treated with hydroxychlorocin alone, and 25% in the control group and on day 6, 100% of patients treated with hydroxychloroquine and Azithromycin were virologically cured, compared to 57.1% patients treated only with hydroxychloroquine, and 12.5% in the control group, both statistically significant follow-ups $p < 0.05$ and $p< <0.001$, respectively. [33]

Showing significant difference in recovery days using Azithromycin in a Sekhavati E. et recluto ECA in 202 patients with COVID-19, where they gave in one case group (n-56) Azithromycin 500 mg orally daily, lopinavir / ritonavir 400/100 mg, twice daily and hydroxychloroquine 400 mg daily, orally; and the control group (n-57) lopinavir / ritonavir 400/100 mg, twice daily and hydroxychloroquine 400 mg daily, orally, for 5 days treatment, with a statistically significant result of a shorter duration of hospitalization in the group of cases vs. control group (4.61 days versus 5.96 days; P x 0.02). [38]

Recommendations are available to indicate Azithromycin as a combination therapy in patients with COVID-19 as referred to by Gautret P, et al. where it concludes according tothe resultsobtained s suggests the combined use of hydroxychloroquine with Azithromycin for its synergistic effect on the treatment of patients with COVID-19, and for the effectiveness of Azithromycin in preventing severe respiratory tract infections when administered in patients with viral infection. [33]

There are ECAs that are in the realization of field work:

- Hinks et al. they are conducting a randomized clinical trial in 800 patients with COVID-19, where they aim to evaluate the effectiveness of Azithromycin 500 mg once daily for 14 days to reduce and/or prevent complications of lower respiratory treatment with follow-up for up to 28 days of follow-up. [39]

- Akram J. et al, are designing a multicenter randomized clinical trial in which seven comparative groups with drugs will be held where Azithromycin will be included as monotherapy and as a triple regimen, performing it in 470 patients, with the outcome that will be a laboratory result with COVID-19 PCR test negative to 7 days of follow-up. [40]

Azithromycin is a consumer drug for SARS-Cov2 (COVID-19) approved by the U.S. Food and Drug Administration. [30]

4.7.3 Rivaroxab

Use and use in COVID-19 patients

SARS studies conclude that initialtreatment with HBPM reduces mortality by 48% at 7 days and 37% at 28 days and achieves a significant improvement in oxygen blood pressure/O2 inspired fraction (PaO2/FiO2) by mitigating microtrombo formation and associated pulmonary coagulopathy. In addition, in studies of critical patients, the use of HBPM decreased the inflammatory condition22. Therefore, studies derived from COVID-19 use HBPM in all cases during admission into prophylactic doses (enoxaparin 40-60 mg/day) for at least 7 days. [41]

The addition of low doses of Ribaroxaban (2.5 mg twice daily) to standard medication in patients after surviving acute coronary syndrome (ACS) was associated with a significantreduction in mortality over an average treatment period of13.3 months. [42]

A beneficial effect of rivaroxaban 2 2.5 mg daily in combination with aspirin (100 mg daily; double-route inhibition; DPI) was then confirmed by the COMPASS Trial ("Cardiovascular results for personas usinganticoagulation strategies") evaluating clinically stable patients with coronary heart disease (CAD), as well as patients with stable periphery arterial disease (PAD) or carotid arterydisease withcoVID-19 symptoms. [42]

Antiviral therapies interact strongly with DOAC (Oral Anticoagulants- Ribaroxaban), because both are substrates of glycoprotein P and /or based on cytochrome P450 metabolic pathways. Therefore, concomitant administration of DOAC And Antiviral Medicinal Products has the potential to dramatically increase DOAC anticoagulant plasma level, which increasesthe risk ofbleeding. [43]

Which obviously speaks of hospitalized patients with a history of consumption, making it viable in outpatients and not for hospitalization. The image can assess the bioavailability that persists in patients with post-hospitalization antivirals + DOAC and the bioavailability of patients with prior use of DOAC prior to hospitalization.

Although the potential of antiviral agents to increase the plasma concentration of DOAC, as well as their risk of bleeding, it is well known that there is no agreement on the most appropriate clinical management in these circumstances. An alternative option might be to adjust thetwo is (when available). [43]

Comparison of Rivaroxaban with low molecular weight heparin Rivaroxaban 10 mg once daily has been compared with HBPM or fondaparinux in more than 12,000 patients in phase III (CANCER COLORRECTAL), randomized studies in the prevention of VTE (venous thromboembolism) after major orthopedic surgery. [44]

In study RECORD 2, 2509 patients scheduled to undergo total elective hip replacement were randomized to receive oral Rivaroxaban 10 mg once daily for 31 to 39 days or enoxaparin 40 mgonce daily via theirbcutaneous for 10-14 days. [44]

Extended prophylaxis with Rivaroxaban reduced the incidence of deep vein thrombosis (symptomatic or asymptomatic detected by bilateral venography), non-fatal pulmonary embolism and mortality from all causes up to days 30–42 (absolute risk reduction 7.3%, CI 95% 5.2–9.4; p <0.0001) without a significant increase in any bleedingduring treatment. [44]

Cancer therapy is predominantly given in the outpatient environment, leaving many cancer patients at extended risk. Two large randomized trials in mixed cancer populations have evaluated extended prophylaxis with heparin event rates and absolute benefit were low, and guidelines recommend routine thromboprophylaxis in such patients. (6)
Rivaroxaban is powerful, oral, highly selective. Direct Xa factor inhibitor and is effective for primary and secondary thromboprofilaxis. [45]

The intercommunication between coagulation and inflammatory pathways has been well documented. Dugina T.N. referred to as protease activated receptors (PAR) comprising 4 subtypes (PAR1 -PAR4) with a mechanism based on a proteolytic binding. The endothelium, platelets, pro-inflammatory cytokines and various proteases |e.g. Tissue factor(TF), Xa factor, thrombin|, through the activation of PAR receptors, are points of contact between these two pathways. [46]

Reducing the production of Thrombin by inhibiting Factor Xareduces plateletactivation, decreases the production of inflammatory cytokines, prevents the progression of atherosclerosis and decreases plaque instability.

Ning Tang and collaborators. refers in its retrospective cross-sectional study with anticoagulant treatment to patients with COVID-19, the D-dimer was greater than 3.0 g/ml (6 times the upper limit of normal, six ULN), finding a reduction of approximately 20% in mortality with heparin treatment (32.8% vs 52.4%, P .017). [47]

In a quasi-experimental study of Guerrero M.I. et al. current phase of termination of discussion and analysis, the null hypothesis is rejected and refers to the case that if there is a change in the frequency of patients recovered from 80 to 90 % in patients diagnosed with COVID-19 after treatment of imperfection Acetaminophen, Ivermectin, Azithromycin, Rivaroxaban in patients with COVID-19 from U.M.F 13 during the July-August 2020 period. [48]

4. Justification

Emerging coronaviruses (CoVs) such as SARS-CoV-2 cause serious diseases in humans and to date there is no approved treatment available for use. In recent months since the SARS-CoV-2 pandemic declaratory worldwide, there have been many initiatives to assess the ability of various drugs against SARS-CoV-2, in addition to current research to develop an effective vaccine. The role of Ivermectin against SARS-CoV has been demonstrated in vitro and it is suggested that it could have an effect against SARS-CoV-2. In an observational study mortality was lower in the Ivermectin group (7.3% versus 21.3%) and overall mortality rates were lower with Ivermectin (1.4% versus 8.5%; HR 0.20 CI 95% 0.11-0.37 p < 0.0001), phase 3 clinical trials are needed to verify these findings, for the benefit of the population under COV-2 SARS disease (COVID-19). Of the anticoagulants Rivaroxaban,according to the effects of inhibition of factor Xa and the formation of Thrombin, goes beyondanticoagulation through interaction with PAR receptors, due to having anti-inflammatory effects, decreasing arteriosclerosis and platelet aggregation. A reduction of approximately 20% in mortality with anticoagulant treatment has been reported. The management of first-level patients for the evaluation of COVID-19 patients the clinical and paraclic evaluation of a suspected or confirmedcase ofCOVID-19, should adhere to current medical practicesaccepted for patients with acute respiratory infections and comorities. So it is essential to determine vital signs and pulse oximetry,theconsultation should be based onsplit decisions. It has been documented that themodel of care, focused on the environment, is more beneficial in terms of understanding, satisfaction, adherenceto treatment and reduction of complications. The technical information thatmatters to you about diagnosis, treatment and follow-up (follow-up and reference consultation) should be transferred to the patient in a clear and simple way, so that the taking decisions is jointly andwell-supported. So within the guidelines for patient care by COVID-19 refers that it is suggested to make a follow-up consultation at 24-48 hours, in application to the "Standardized GuidelineforSurveillance and Requestology and by COVID-19 Laboratory", especially in patients of high riesgo. So an outpatient monitoring model for patients with COVID.19 carried out by the Deconcentrated Administrative Operation Body of the Northern Federal District of the Mexican Institute of Social Security (I.M.S.S.) considering the use of Information and Communication Technologies, to minimize risk of contagion in top-level health care personnel is necessary to cover in the patient terms of understanding, satisfaction, adherenceto treatment and reduction of complications. So evaluate in patients by COVID-19, in mild phase or newly diagnosed, especially in those at high risk for having comorities, the benefits of a patient-centered care model, in which important technical information on diagnosis, treatment and follow-up is transferred to you in a clear and simple way.

This care model involves outpatient monitoring, which considers the use of Information and Communication Technologies (video call monitoring), to minimize the risk of contagion in first-level health care personnel and to improve the patient's understanding, satisfaction, adherence to treatment and reduce complications.

5. APPROACH TO THE PROBLEM

Lto coronavirus disease (COVID-19) is caused by SARS-COV2 and represents thecausalagent of a life-threatening disease potential that isa major global public healthproblem. Person-to-person transmission of COVID-19 infection led to the isolation of patients who subsequently received a variety of treatments. Extensive measures to reduce human-to-humantransferof COVID-19 have been implemented to control the current outbreak. [50]

This has forced rapid action not only to try to contain the advancement of contagions, but also to develop protocols of action that reduce mortality. [51] Drugs such as Ivermectin inrelation to the safety of this drug are approved for human use by the FDA for various parasitic and skin infections, it has been proposed in pharmacokinetic simulations that for possible management of patients with COVID-19 las doses should be high, thereare severalstudies in which high doses of Ivermectin have been shown to have commptable safetyat standarddoses. [52.53] However, there is a study in Lima, Peru,which reports the therapeutic safety of Ivermectin in humans with COVID-19 and describes a significant decrease in the fatality rate of 6.1 times lower compared to patients who did not use Ivermectin (1.4 vs. 8.5% , $p< 0.0001$). [31] Clinical trials are in the recruitment phase where Ivermectin is used for the treatment of COVID-19 infection. [32] WHO and PAHO encourage the use of unproven therapies in the context of a randomized clinical trial (CCA). [28] Anticoagulants have reported up to 20% in reducing mortality (heparin), Ribaroxaban is effective with inhibition of PAR1/PAR2/PAR4 receptors through X Factor blockage and Thrombin formation, have anti-inflammatory effects, decrease arteriosclerosis and platelet aggregation. [46.47]

Karen Donelan's reports in a cross-sectional study, which referred to 254 people visited by Telemedicine for 15 minutes, referred with answers > 90% with "if, definitely agree" rating, in explaining things in an easy-to-understand way, whether patient care was heard and whether she felt that the doctor had spent enoughtime on the patient when making the video call. [49] A Specific Telemedicine Working Method is being carried out

during Phase 3 of COVID-19 contingency in IMSS rightholders to followup patients with clinicaldiagnosis, confirm orand graduates of COVID-19 fromoperation Administrativa Dfocused on Northederal F-D,within the specificobjectives is to detectearly signs and symptoms of possiblecomplications as well as to offer a policy of early intervention treatment in top-level rightholders. [20]

Considering also what was reported by Guerrero M.I. et al., 48 in a quasi-experimental study in the current phase of completion of discussion and analysis where there is a change in the frequency of patients recovered from COVID-19 of 80-90% after an early intervention treatment (paracetamol, Ivermectin, Azithromycin , Rivaroxaban) of UMF 13 during the period of July-August 2020. It is necessary to carry out a double-blind randomized clinical trial where a treatment (Azithromycin / Ivermectin / Ribaroxaban / Paracetamol) of early intervention (during the first 5 days of COVID disease -19) in patients entitled to the first level of care performing monitoring with video calls, the following research question is formulated:

Research question

What is the percentage of patients who change their clinical evolution in patients with COVID-19 under treatment with Azithromycin / Ivermectin / Ribaroxaban /Paracetamol vs. Azithromycin / Ribaroxaban / Paracetamol followed by video call for 14 days from U.M.F 13 and U.M.F 20 from I.M.S.S., in the period December 2020- February 2021. ?

6. Objective

General Objective.

- Evaluate the percentage of patients diagnosed with COVID-19 who modify their clinical evolution under an early intervention comparative treatment in U.M.F 13 and U.M.F 20 U.M.S.S. speakers during the period December 2020- February 2021.

Specific objectives.

- Describe sociodemographic characteristics (sex, age, schooling, occupation, marital status) in patients with COVID-19 under treatment with Azithromycin / Ivermectin / Ribaroxaban /Paracetamol vs. Azithromycin / Ribaroxaban / Paracetamol followed by video call for 14 days from U.M.F 13 and U.M.F 20 from I.M.S.S., in the period December 2020- February 2021.
- Record laboratory results performed in patients with COVID-19 under treatment with Azithromycin / Ivermectin / Ribaroxaban /Paracetamol vs. Azithromycin / Ribaroxaban / Paracetamol followed by video call for 14 days from U.M.F 13 and U.M.F 20 from I.M.S.S., in the period December 2020- February 2021. .
- Evaluate adverse drug reactions for follow-up days in patients with COVID-19 under treatment with Azithromycin / Ivermectin / Ribaroxaban /Paracetamol vs. Azithromycin / Ribaroxaban / Paracetamol followed by video call for 14 days from U.M.F 13 and U.M.F 20 from I.M.S.S., in the period December 2020- February 2021.
- Estimate clinical symptoms per follow-up days in patients with COVID-19 under treatment with Azithromycin / Ivermectin / Ribaroxaban /Paracetamol vs. Azithromycin / Ribaroxaban / Paracetamol followed by video call for 14 days from U.M.F 13 and U.M.F 20 from I.M.S.S., in the period December 2020- February 2021.

7. WORKING HYPOTHESES

- **Null Hypothesis: There will be no change** in clinical evolution ≥ 25 % of patients diagnosed with COVID-19 under early intervention treatment with Azithromycin/Ivermectin/Ribaroxaban/ Paracetamol vs. Paracetamol. Azithromycin/Ribaroxaban/ Paracetamol for 14 days followed by video call from U.M.F 13 and U.M.F 20 from I.M.S.S., during the period December 2020- February 2021.

- **Alternative hypothesis: If there will be a change** in clinical evolution ≥ 25 % of patients diagnosed with COVID-19 under early intervention treatment with Azithromycin/Ivermectin/Ribaroxaban/ Paracetamol vs. Paracetamol. Azithromycin/Ribaroxaban/ Paracetamol for 14 days followed by video call from U.M.F 13 and U.M.F 20 from I.M.S.S., during the period December 2020- February 2021.

8. MATERIAL AND METHODS

a) Study place:

The study will be carried out in Family Medicine Unit No. 20 and in the U.M.F 13/H.G.O., Units belonging to the North Deconcentrated Administrative Operating Body D.F. of the Mexican Institute of Social Security.

b) Study groups: Two groups of patients with COVID-19, a group called A that will receive treatment with Azithromycin,paracetamol, Ivermectin and Rivaroxaban and the group called B to be treated with acetaminophen, Azithromycin and Rivaroxaban, will beintegrated.

c) Study Design: Randomized experimental study, simple blind, prospective, longitudinal and open.

d) Inclusion Criteria:

- Right-speaking Patients of Family Medicine Unit No.20 and Family Medicine Unit No.13 belonging to the Northern DF of the IMSS.
- Male and female patients
- Patients over 18 years of age.
- Patients with COVID-19 operational definition compliance and confirming P.C.R. test. positive within the first few days of the disease (which are evaluated at the first level of medical care).
- Patients with comorities such as Type 2 Diabetes Mellitus, Systemic High Blood Pressure, Overweight or Obesity.
- Accepting to sign informed consent
  - **Related to the Video Call:**
- ImSS Family Medicine Unit No.20 and Family Medicine Unit No.13 belonging to imSS North DF have Electronic Equipment Installation for Internet use.

e) Exclusion Criteria:

- Patients with severe COVID-19 (Ameriten sent immediate to second level of care, hospital)
- Patients with any Pathological Personal History of Haematological Diseases.
- Patients allergic to macrolides (Azithromycin) and Ivermectin.

Sample size and sampling.

It is performed for sample size calculation, the Difference of Proportions formula presented inDr. Talavera JO et. [49] and according to laboratory modification values in PATIENTS with COVID-19 of the randomized clinical trial study of Gautret P. Et al. [33] where group A of patients was treated with azithromycin/hydroxychloroquine and the second group B was treated with hydroxychloroquine. By evaluating laboratory modification in COVID-19 patients after 4 days the proportion of patients who managed to modify it obtained a modification difference of 25%.

La fórmula para la determinación del tamaño de muestra para diferencia de proporciones es:

$$n = \left[\frac{Z_\alpha \sqrt{2\pi_1(1-\pi_1)} - Z_\beta \sqrt{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)}}{\pi_1 - \pi_2} \right]^2$$

Assuming that for the study problem, group A of patients receiving treatment with Ivermectin /Azitromycin/ Ribaroxabán /Paracetamol is expected to succeedin 50% of cases, while group B will be treated with Azithromycin / Ribaroxaban / Paracetamol to succeed in 25% of cases, the values in the formula will be replaced as follows:

Where:
Za= (a= 0.01) 2.576
Zb = (b= 0.10) – 1.645
P1= 0.50
P2= 0.25
P1 - P2 = 0.25

No. 25.97 **- 26**

Plus 20% losses n. 31.2 **x 31** patients are needed in the study. Group formation:

The above result has to be rounded to the upper digit. In this way, the sample should include 31 subjects in each study group if one wants to have a 90% chance (90% power) to detect at least a 25% difference in the success rate of clinical evolution modification between the two treatment groups that are exemplified.

Random numbers generated by draw will be used for the formation of the groups in which the patient arriving will take a piece of paper which will have the number of the group to which it will be assigned. With a type of block randomization, A (Azithromycin, acetaminophen, Ivermectin and Ribaroxaban) andB (acetaminophen, Azithromycin, and Ribaroxaban), each 31 participants.

The mechanism used to implement the random mapping sequence was the use of two containers that will include 31 blue boxes and another 31 orange with color identification to the assigned treatment, to be performed by an intern doctor.

The staff who generated the random assignment sequence will be an intern physician (it will be their only role in the study protocol) and who selected the participants and assigned the participants to the interventions will be an associate researcher (it will be their only role in the study protocol).

He remained blinded after assigning the interventions to the given patient unknown to what treatment he is receiving and to the assigned treatment group A or B.

VARIABLES

1.- DEMOGRAPHIC VARIABLES

Age

Conceptual definition: Period of time elded from birth in years

Operational definition: It shall be measured through a Questionnaire carried out at the beginning of the study with unarmed consent foreach of the two groups considered agereached in years at the start of the study. (See Annex 2)

Variable type: Qualitative categorical

Measurement scale: years 1) 40-50 years 2) 51-60 years 3) 61 – 70 years

Sex

Conceptual definition: Phenotypic and genotypic characteristics that identify the

Individual as male and female

Operational definition: It will be measured through a Questionnaire carried out at the beginning of the study withunarmed consent for each of the two groups considering sex atthe beginning of thestudyor. (See Annex 2)

Variable type: Nominal dichotomous qualitative

Measuring scale: 1) Male 2) Female

Marital status

Conceptual definition: A particular condition that characterizes a person in what makes their personal bonds with individuals of another sex or of the same sex.

Operational definition: It shall be measured through a Questionnaire carried out at the beginning of the study withunharmed consent for each of the two groups considering the civil situation at the time of the study. (See Annex 2)

Variable type: Nominal dichotomous qualitative

Measuring scale: 1) Single. 2) Married. 3) Widow. 4) Separated. 5)Free Union 6) Divorced

Occupation

Conceptual definition: The type of work you do that generates economic resources

Operational definition: It shall be measured through a Questionnaire carried out at the beginning of the study with unarmed consent foreach of the two groups considering the occupationat the time of the study. (See Annex 2)

Variable type: Nominal dichotomous qualitative

Measuring scale: 1) Part-time work. 2) Full-time work. 3) Housewife 4) Pensioned 5) unemployed 6)Ortro

Schooling

Conceptual definition: years studied and approved in some type of educational establishment.

Operational definition: It will be measured through a Questionnaire conducted at the beginning of the study withunarmed consent for each of the two groupsconsidering schooling at the beginning of the study. (See Annex 2)

Variable type: Nominal dichotomous qualitative

Measuring scale: 1) Sinstudies 2)Pre-school 3)Primaria 4)Secundaria 5)Prestorative or baccalaureate 6)Carrera técnica 7)Licenciatura 8)Otros

2.- INDEPENDENT VARIABLE

Patients with 2V-2 SARS (COVID-19)

Conceptual Definition: A viral disorder characterized by Headache, Cough, Fever, Conjunctivitis, Myalgias, Arthralgias, Rhinorrhea, Odinophagia, Anosmia, Chest Pain, Dyspnoea and other symptoms of VIRAL NEUMONIA, caused by an agent known as Coronavirus SARS-CoV-2 dthe genusBETACORONAVIRUS .

Operational Definition: Confirming PCR tests will be performed on all patients with suspected VF-2 SARS (COVID-19).

Variable Type: Qualitative

Measuring scale: Nominal

Measuring Unit: SARS 2 Patient (COVID-19).1, Suspected Patient SARS 2 2 (COVID-19) ..

3.- DEPENDENT VARIABLE

Changing clinical developments

Conceptual Definition: Registration of clinical health conditions as symptoms (Headache, Cough, Fever, Conjunctivitis, Myalgias, Arthralgias, Rhinorrhea, Odinophagia, Anosmia, Chest Pain, Dyspnoea), Adverse Reactions (Diarrhoea, Nausea, Vomiting, Disorientation, Dizziness, Asthenia, Equimosis/Petechiae, Vertigo, Tinnitus, Urticaria, Hemorrhage, Angioedema, Palpitations, Chest pain) and laboratories(hematic biometrics, C-reactive protein, Dimero-D, ferritin, prothrombin time, thromboplastin time, lactic dehydrogenase) of patients with Covid-19 Mild Clinical Phase performed through monitoring (See Table 1) for 14 days of approx. lasting 15-20 minutes, following administration in two group (A and B) of Azithromycin/Ivermectin/Ribaroxaban/ Paracetamol vs. Azithromycin/ Ribaroxaban/ Paracetamol (See Table 4).

Operational Definition: The patient with the presence of COVID-19 confirmed by PCR test to participate in the study, the granting of the medicinal product randomly to belong to group A or B, is initiated after the signing of informed consent (Annex1), Azithromycin/Ivermectin/Ribaroxaban/ Paracetamol vs. Azithromycin/ Ribaroxaban/ Paracetamol (See Table 4),to be followed for 14 days by video call (15 to 20 min approx. daily) to the patient and the presence or absence of clinical symptoms, adverse reactions and laboratory registration is recorded daily.

Variable Type: Qualitative, Quantitative (Laboratories)

Measurement scale: Nominal, Interval (laboratories)

Measurement Unit: Symptoms of fever, cough, headache, myalgias, odinophagia, anosmia, rhinorrhea, arthralgias, chest pain, dyspnoea, conjunctivitis)-1 (SI), 0 (NO).

Adverse reactions 1 (SI), .0 (NO).

Laboratories - continued reason

Overview of the Study (see Figure 1 and 2).

1.- Project management

(a) Communication with clinical department heads and directors for the authorization of instrumentation.

You will go to U.M.F. No.20 with the director of U.M.F No. 20 and the director of the U.M.F. No. 13 for the authorization of the implementation of the research project.

b) Recruitment of pollster staff

Six U.M.F. passing doctors will be assigned. 20 and 7 U.M.F. passing doctors. 13 to serve as a pollster.

c) Training of project surveyor staff.

The surveyor staff will be trained by the project manager in Classroom 1 of the U.M.F. 20 with a duration of 2 hours where it will be reported on:

-Identify the intern physician to patients who are diagnosed with COVID-19 confirmatory testing with care in family medicine unit No. 13 and No. 20 of the IMSS, based on the case notification by the Epidemiology service, meeting the criteria of inclusion of the study, you are called by telephone so that upon informed consent and your signature if you agree to be part of the study, a triptych of home care is granted for patients with COVID-19 and early intervention treatment medicine.

-Guidelines for the patient who is identified by the family doctor who is based on the COVID-19 response teams, meeting the criteria of inclusion to be granted informed consent and signature if he agrees to be part of the study, as well as a triptych of home care for patients with COVID-19 and early intervention treatment medication. (See Annex 1)

- The characteristics of the video call made via Wi-Fi every 24 hrs for 14 days lasting approximately 15 to 20 minutes and question the patient about the major and minor symptoms of COVID-19 disease, adverse reactions, dyspnoea and symptom information and warning signs for reference to the second level of care will be disclosed to the intern. (See Annex 2)

2.-Fieldwork

The study will be conducted in the family medicine unit (U.M.F. No. 13 and No. 20 of the IMSS, according to the sample size for convenience entering the U.M.F 20 during the period of November-December 2020, captured by the COVID-19 respiratory module service, making video calls by intern doctors, contemplating 15 minutes of video call per patient , lasting approximately 3 total hours per day of care for each intern. Video call times will be open within 8:00 a.m. to 8:00 p.m.

2.1. Interview plan

For the first interview of each patient will be given a space of 15 minutes that will be aimed at explaining in a general way what is the monitoring of the clinical status with video calls, and interrogate about personal data (identification sheet and personal history), all with prior presentation by the interviewer (indicating full name, position and category, unit of which the call is made and name of the protocol).

Subsequently, it shall follow the entire symptomatology section, which will ask what is set out in Annex 1, first symptomatology of the operational definition for COVID-19 (to assess whether there is improvement or clinical deterioration), and adverse effects of medicinal products (if it has any of those mentioned in Annex 1).

At the end of questioning about the symptomatology the interview will be terminated, explaining in advance to the patient that the number of which the call was made should not be used for any reason other than for the scheduled video calls, and that if he/she were to present any symptoms of severity he should go to the emergency department closest to his home , this is because video calls are for research purposes only.

Interviews are with a scheduled follow-up of 14 days from day 1, reminding the patient on the 14th that it will be the last day of follow-up of symptomatology, and that if it were to present any symptoms of severity from this day, the indication will be the same as that mentioned from day 1 (go to the emergency department assessment).

At the end of the interview follow-up each interviewer will append the information to a database so that they can then perform analysis of the information.

2.2 **Delivery of medicine.**

The patient is informed via video call that meets the criteria of inclusion and prior signature of informed consent to go to UMF No.13 for the randomized delivery of the medicinal product that will be wrapped in blue paper with the written legend of drug consumption according to Table 4 (described in this protocol), this procedure is performed by the intern doctor, which is known as group A (experimental) Azithromycin,acetaminophen, Ivermectin and Rivaroxaban and group B (control) acetaminophen, Azithromycin, and Rivaroxaban.

Group formation:

For the formation of the groups the simple blind randomized sampling method will be used in its draw mode in which the patient arriving will take a piece of paper which will have the number of the group to which it will be assigned, group A Azithromycin,acetaminophen, Ivermectin and Rivaroxaban and group B acetaminophen, Azithromycin,and Rivaroxaban.

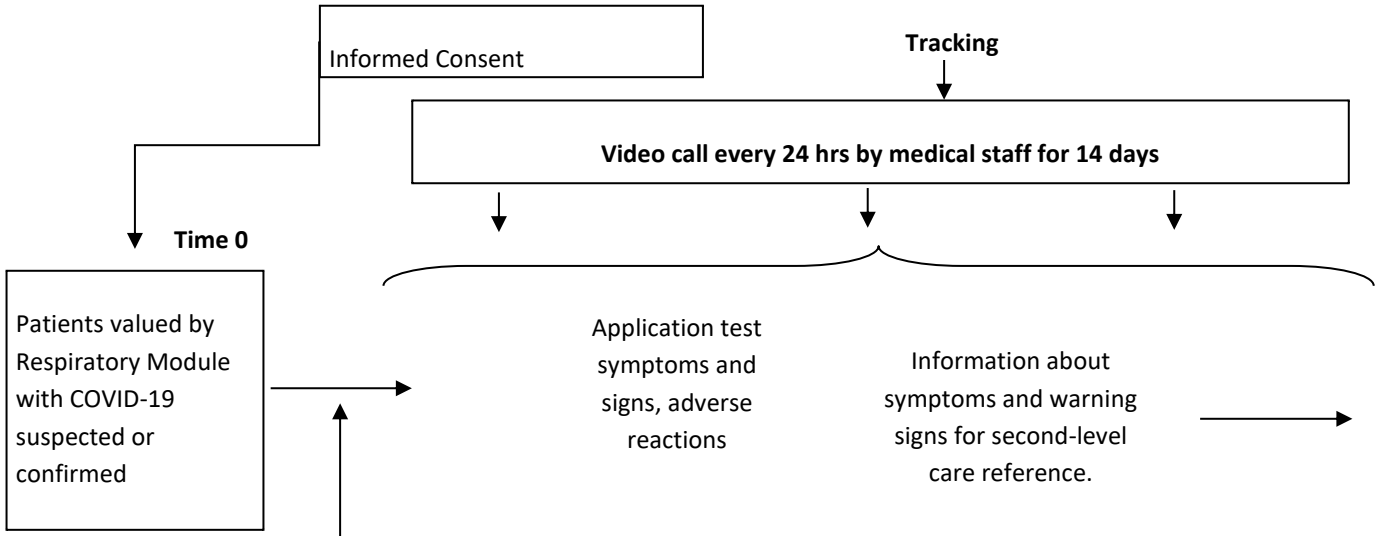
2.3 **Taking laboratories**

Wi-Fi video call will be given the indication of conducting laboratories (hematic biometrics, C-reactive protein, Dimero-D, ferritin, prothrombintime, thromboplastin time, lactic dehydrogenase) taken at the start of treatment and on day 21 of the disease by laboratory personnel in HGZ 48 of the IMSS.

3.- Final evaluation

Video call tracking is terminated by meeting 14 days of follow-up of patients in the study or until you have at least 7 days with reduced symptoms and signs of COVID-19.

Fig. 1 Study Design Description Part 1



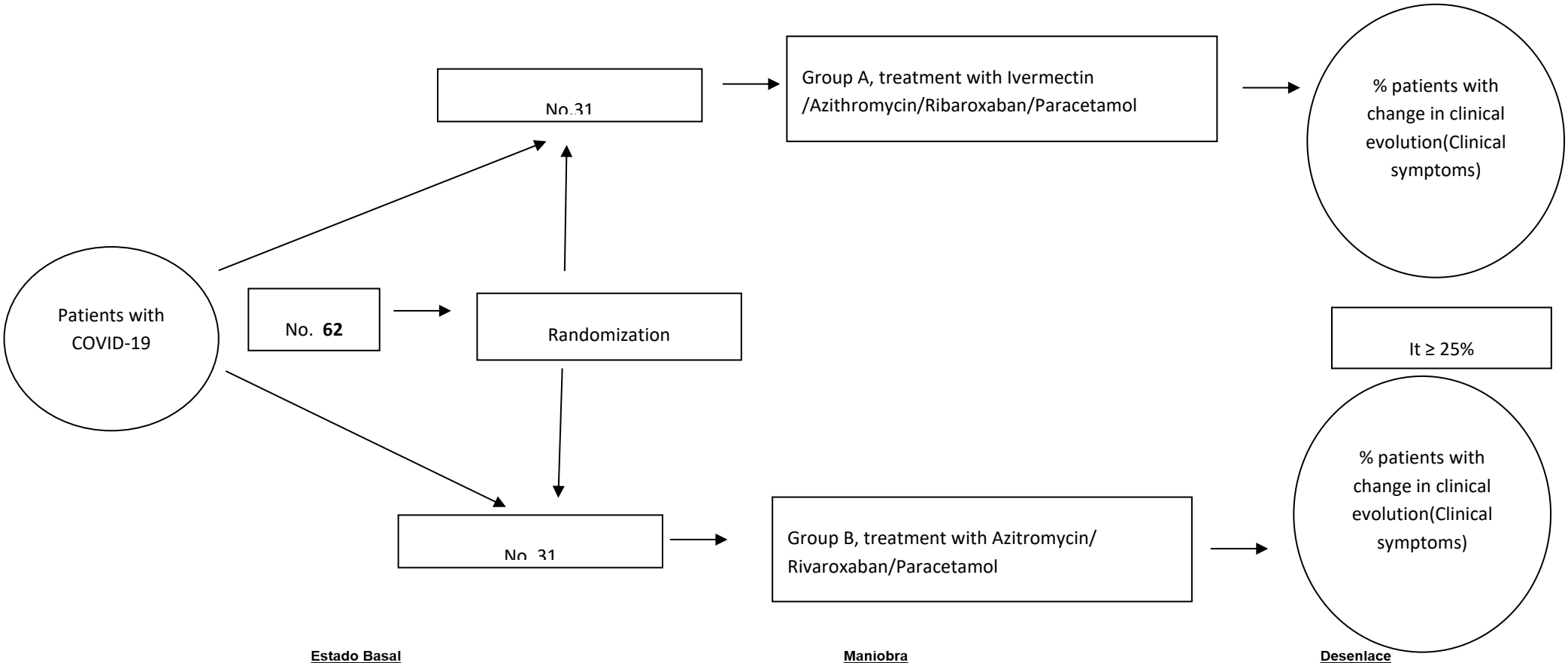
Delivery of medicines to patients Confirmed COVID-19 , paracetamol, Ivermectin, Rivaroxaban, Azithromycin.

Medication	Dose	Range	DURATION (DAYS)
PARACETAMOL 500 mg TAB	500 MG VIA ORAL	EVERY 8 HRS IN CASE OF FEVER > 38th C	3 DAYS
AZITROMICINA 500 mg TAB	500 MG VIA ORAL 250 MG VIA ORAL	EVERY 24 HRS EVERY 24 HRS	FIRST DAY SECOND TO FOURTH DAY
IVERMECTINA 6 MG TAB	2 TABLETS < 80 KG VIA ORAL 3 TABLETS between 80-110 kg VIA ORAL 4 TABLETS > 110kg VIA ORAL	EVERY 24 HRS	2 DAYS
RIVAROXABAN 10MG	1 TABLETA VIA ORAL	EVERY 24 HRS	10 DAYS

Triptic delivery of "DOUBTS YOU MAY HAVE DURING **THE INTERVIEW TRANSCURS**

"

Fig. 2 Study Design Description Part 2



Estado Basal

Demarcación Diagnóstica

Universo de trabajo:

- Unidad de Medicina Familiar N.20 y U.M.F. 13

28 pacientes registrados de Septiembre a Octubre 2020

Criterios diagnósticos:

- Pacientes confirmados con prueba PCR positiva COVID-19
- *Criterios de selección :*

Pacientes derechohabientes de la U.M.F 20 y U.M.F. 13

- Diabetes Mellitus Tipo 2, Hipertensión Arterial Sistémica, Sobrepeso, Obesidad, > 18 años

Estratificación Pronostica

- *Cronométrica*:
- Entre el día 1 al 7 de enfermedad COVID-19 con Prueba PCR positiva

- *Clínicos:*
- Sobrepeso
- Obesidad

Maniobra

Aplicación adecuada de la Maniobra

- Previa firma de consentimiento informado, se toma a paciente prueba de PCR por personal de laboratorio, posteriormente a las 24 hrs de obtener el resultado de prueba de PCR, siendo positivo el paciente, se le llama telefónicamente para que acuda el familiar por solicitud de laboratorio y se entrega el tratamiento (otorgado en forma aleatoria). Posteriormente se le hará seguimiento por videollamadas a los pacientes por personal medico (previamente capacitado) interrogando sintomatología COVID-19, reacciones adversas durante 14 días.

Maniobras periféricas iguales y adecuadas

- Toma de Biometría Hemática Completa, Proteína C reactiva, Tiempo de protrombina, Tiempo de tromboplastina activado, Deshidrogenasa Láctica, Ferritina, Dimero – D, en ambos grupos, por personal de laboratorio del H.G.Z 48(confirmar por correo electrónico un día previo a la asistencia del paciente a las 8:30 am)

Desenlace

- Percentage of patients with clinical evolution modification (Clinicalsymptoms) group A and B.
- Percentage of patients with adverse reactions group A and B.
- Registration oflaboratory rultados group A and B.

14 days of video call tracking

STATISTICAL ANALYSIS

Assuming an 25% effectiveness in modifying clinical evolution(symptoms of fever, cough, headache, myalgias, odinophagia, anosmia, rhinorrhea, arthralgias, chest pain, dyspnoea, conjunctivitis) of patients diagnosed with COVID-19 under early intervention comparative treatment for 14 days followed by video call, with a potency of 90%, an error rate type I of 1% and a follow-up loss of 20%; we calculated a total of 62 patients with COVID-19, i.e. 31 cases in group A with treatment of Azithromycin/Ivermectin/Ribaroxaban/ Paracetamol and 31 in group B with Azithromycin/Ribaroxaban/ Paracetamol treatment would be necessary for analysis. Statistical differences were assessed by Pearson's hi-square Ctest or Fisher's exact Prueba as categorical variables, as appropriate. The scans will be performed in SPSS version 21.

9. ETHICAL ASPECTS

RISK OF RESEARCH.

As mentioned in the regulations of the General Health Law, article 17, on health research, this research will be category 1, since this investigation does not present any risk to the patient, since informed consent prior to the indication of the medicinal product is signed and that the patient agrees to take the drug.

CONTRIBUTION AND BENEFITS OF STUDY FOR SOCIETY.

On the other hand, this research will help to identify in an appropriate and timely manner the coVID associated factors as doctors perform interventions to delay or decrease the development of this pathology.

Confidentiality.

The information collected in the clinical records will not obtain the patient's name in order to keep the patient confidential.

FORM OF PATIENT SELECTION.

The review of previously diagnosed patient records with the criteria for inclusion of this investigation shall be carried out.

This research was conducted in accordance with the guidelines and rules governing research in Mexico and the world:

HELSINKI DECLARATION 1964

This statement is based on the review of research by an ethics committee, in turn giving rise to new ethics committees for research at the international level. This research is classified in category I, where no intervention is performed, so it does not meet the criteria to be submitted to an ethics committee.

MEXICAN OFFICIAL STANDARD 012 SSA 3-2007.

This standard sets out the criteria for the implementation of human health research, specifies how research review and approval should be carried out in health institutions, in order to protect the rights and well-being of participants.

This research took this standard into account, applying only in some respects, as it will be a retrospective investigation, analyzing clinical records.

Finally, the general guidelines for conducting research at the Mexican Institute of Social Security were considered, highlighting the following: "that any research carried out in the institute must show a deep respect for the person the life and security of all the rights that who participate in them by following the institutional rules in this matter", in particular by the Organization Manual of the Head of Teaching and Research Services (Agreement No. 15; 6 - 84 of 20 June 1984 of the Honourable Technical Council).. [38]

10. Physical and Financial Resources

To carry out this study protocol, UMF 20 facilities of the Mexican Social Security Institute were used, with the following resources:

- **HUMANS:** Five researchers; Eleven intern physicianswill participate in the study protocol during the data collection period through the filling of the data collection instrument and the realization of the database of patients receiving COVID-19.

- **TECHNOLOGICAL:** Two Hp 1502 computer equipment with Word and Power Point 2015 program used for information collection and writing of the study protocol, as well as for the analysis of results; OKI printer used for the printing of questionnaires and informed consents; access to the external consultation network and comprehensive family medicine system used to obtain information from the electronic clinical record of participating patients or, where appropriate, the realization of data collection sheet.

- **PHYSICAL:** Teaching classroom, confidentiality letter, informed consent format, two support tables, four pens, printing paper and fifteen cell phones. You will also have the Triage area for the delivery of the drug which has the drug kit a doctor and a nurse.

The aforementioned resources are provided by the IMSS without increasing the demands and inputs available in the medical unit.

11. Timeline of protocol activities

" PRONOSTIC MODIFICATION IN PATIENTS WITH COVID-19 UNDER EARLY INTERVENTION TREATMENT IN U.M.F 13 AND U.M.F 20".

	March 2020	April 2020	May 2020	June 2020	July 2020	August 2020	September 2020	October 2020	November 2020	December 2020	January 2021	February 2021
Delimitation of the subject to be studied	R	R	R									
Establish the title of the investigative protocol	R	R	R									
Recovery, review and selection of the bibliography.	R	R	R	R	R	R	R					
Ask research question	R	R	R	R	R							
Elaboration of the Theoretical Framework.	R	R	R	R	R	R	R					

Conducting justification approach to the problem and objective of study and working hypotheses	R	R	R	R	R	R	R					
Preparation of Materials and Methods, Ethical Aspects.	R	R	R	R	R	R	R					
Sent the protocol to (CNIC) SIRELCIS to request registration								P	P			
Collecting information										P	P	
Analysis and discussion of results											P	
Final report writing												P

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14. Annexes

Annex 1

MEXICAN SOCIAL SECURITY INSTITUTE

EDUCATION, RESEARCH UNIT

AND HEALTH POLICIES

COORDINATION OF HEALTH RESEARCH

INVITATION TO PARTICIPATE IN THE PROTOCOL

Ihereby extend to you a cordial invitation to participate in this protocol entitled "PRONOSTIC MODIFICATION IN PATIENTS WITH COVID-19 UNDER AN EARLY INTERVENTION TREATMENT IN THE U.M.F 13 AND U.M.F 20", that you intend that if you have positive COVID19 testing during the onset of the disease, you will be given the opportunity to receive pharmacological treatment for COVID-19, considering for your clinical follow-up of the disease the use of video calls via "WhatsApp" for 14 days, by medical personnel, granting you the benefit if this protocol successfully results in an improvement of symptoms and signs of COVID-19 disease and thus avoid complications thereof; in the same way you are granted these benefits for the whole population that in the future suffers from this disease. On the other hand you are free to leave treatment for any reason you consider disagreeing to remain in protocol.

MEXICAN SOCIAL SECURITY INSTITUTE

EDUCATION, RESEARCH UNIT

AND HEALTH POLICIES

COORDINATION OF HEALTH RESEARCH

Informed consent letter for participation in research protocols (adults)

Study Name:	PRONOSTIC MODIFICATION IN PATIENTS WITH COVID-19 UNDER EARLY INTERVENTION TREATMENT IN U.M.F 13 AND U.M.F 20.
External Sponsor (if applicable):	DOESN'T APPLY
Place and date:	Family Medicine Unit No. 20, Vallejo Causeway 675 cabbage. Magdalena de las Salinas México D.F. Gustavo.A.Madero Delegation and Family Medicine Unit No. 13, Villa Azcapotzalco between Hidalgo and Aztecs, Azcapotzalco Delegation. a____ de_____, 2020.
Institutional registration number:	Slope
Justification and objective of the study:	Coronavirus, known as SARS-CoV2, is a serious disease in humans and to date there is no approved and distributed treatment for its use. In recent months there have been many initiatives to assess the capacity of various medicines against SARS-CoV 2. Drugs such as Ivermectin are known for its antiparasitic activity, however it has been evaluated in recent years for its activity in laboratory studies against various viruses such as yellow fever, among others. This medicinal product has been granted in patients with COVID-19 showing considerable benefit however it is recommended to perform research protocols with greater confidence in order to consider it for administration. Similarly, the well-known antibiotic Azithromycin has shown benefits in COVID-19 patients. The drug named Rivaroxaban, is an anticoagulant that also has anti-inflammatory action as well when administered in patient COVID-19 has reported a decrease in mortality in patients with COVID-19, however it is recommended to perform research protocols to give you greater confidence in its administration. The objective of the study is to evaluate the percentage of patients diagnosed with COVID-19 who modify their clinical evolution under a comparative treatment of early intervention in rightholders of the U.M.F 13 and U.M.F 20 of the I.M.S.S., during the period December 2020-February 2021.
Procedures:	If you participate in this post-POSITIVE COVID19 study, you will be instructed to take medications according to the groups to be handled and will be in accordance with those prescribed by the research physician, could be **from Group A** with taking the following medicines: Acetaminophen 500 mg orally 1 tablet every 8 hrs for 3 days in case of fever equal to or greater than 38.3oC, Azithromycin tablets of 500 mg will take 1 tablet single dose on the first day and then half a tablet (250 mg) orally every 24 for 4 days, Ivermectin 200mcg tablets which will be calculated according to your weight and dosage, will be every 24 hrs for 4 days and Rivaroxaban tablets of

	10 mg will take 1 every 24 hrs for 10 days. If you have Group **B you** will take Paracetamol 500 mg orally 1 tablet every 8 hrs for 3 days in case of fever equal to or greater than 38.3oC, Azithromycin 500 mg tablets will take 1 tablet single dose on the first day and then half a tablet orally every 24 for 4 days and Rivaroxaban 10 mg tablets will take 1 every 24 hrs for 10 days. Also during the taking of medicines and subsequently until 14 days you will be video call daily at a time of 10 am to 14 pm, including Saturday and Sunday to know how your clinical symptoms are, adverse reactions to drugs related to COVID19, duration of this video call will be approximately 15 minutes through your cell phone using the video call via WhatsApp. During the first day of your participation in the protocol you will be informed to attend IMSS Zone General Hospital No.48 at 8:30 am, in the laboratory area for the extraction of 5 milliliters blood and perform hematic biometrics, C-reactive protein, D-dimer, ferritin, prothrombin time, thromboplastin time and lactic dehydrogenase.
Possible risks and discomfort:	By participating in this study and taking medications for 14 days you may have allergy to some of these medications or some other symptoms such as diarrhea, nausea, vomiting, disorientation, dizziness, asthenia, equations, petechiae, vertigo, ringing of ears, intestinal bleeding, angioedema, palpitations, hives, chest pain. Upon surveillance by the video call you can report any inconvenience and be able to give the handling or indication for second level shipping.
Possible benefits you will receive when participating in the study:	No economic, service or drug benefits will be received outside of the that indicate when you participate in this study. By getting adequate results of improvement of symptoms clinicians and avoid the complications of patients with COVID19, the benefits will be for the entire population that in the future suffers from this disease, the drug can be granted initially in our family medicine units.
Information on treatment results and alternatives:	If during your participation there are also new reports of medicines better than indicated are reported or when the request to suspend any for serious effects will also be given the indication of immediate suspension to avoid any damage.
Participation or withdrawal:	Participation in this study is voluntarily subsequent in providing procedural information, possible risks and discomfort. If you decide to participate by signing this informed consent and subsequently decide to withdraw you can do so at the time you decide without any impact on the services you receive within the IMSS or any retaliation. After the withdrawal in case you decide all the data provided and video call will be deleted.
Privacy and confidentiality:	The data provided and when the results of this study are published, no information will be given that could reveal your identity. Your identity will be protected and hidden. In case you request your results it will only be done in a personalized way to protect your identity we will assign you a folio number or code and with it you can request your results by appointment.

Consent Statement:

After I have read and explained all my doubts about this study:

☐	I do not agree to participate in the study.
☐	If I agree to participate in the study

In case of doubts or clarifications related to the study, please contact:

Investigator or Responsible Investigator:	Dr. Gilberto Cruz Arteaga . Clinical Coordinator of Education and Research in Health Enrollment 99351417, Enrollment Family Medicine Unit 20. Calzada Vallejo 675 Col. Nueva Vallejo,C.P. 07750 Mayor Gustavo A. Madero.,CDMX Tel 53 33 11 00 Ext. 15320 and 15368. E-mail: gilberto.cruz@imss.gob.mx

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Collaborators:

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In case of doubts or clarifications about your rights as a participant you can contact: Local Committee of Ethics of Health Research of the ICU of the ICS of the IMSS: Avenida Cuauhtémoc 330 4th floor Block "B" of the Congress Unit, Colonia Doctors. Mexico City, CP 06720. Phone (55) 56 27 69 00 extension 21230, email: comiteeticainv.imss@gmail.com

Name and signature of the participant

Name and signature of who gets consent

Witness 1

Witness 2

Name, address, relationship and signature

Name, address, relationship and signature

Key: 2810-009-013

Annex 2

MEXICAN SOCIAL SECURITY INSTITUTE

EDUCATION UNIT, RESEARCH

AND HEALTH POLICIES

COORDINATION OF EDUCATION AND HEALTH RESEARCH

Identification format, laboratory follow-up, clinical symptoms and adverse **reactions**

Date: _____

A. Demographics

1.1 Number

1.2 Social Security Number _____

1.3Phone. _____

1.4 Age _____ years

1.5 Sex

Female	Male

1.6 Marital status.

Single	Married	Free Union	Widower	Divorced(a)	Separated)

1.7 Schooling

Illiterate	Preschool	Primary	Secondary	High School/ High school	Technical career	Licenciatura	Other

1.8 Occupation

Half-day	Full day	Housewife	Pensioner	Unemployed	Other

1.9 Treatment

Azithromycin/Ribaroxaban/Paracetamol	0
Azithromycin/Ivermectin/Ribaroxaban/Paracetamol	1

1.10 Disease Start Day/ Start Day of Treatment

Day/month/year	Day/month/year

1.11 Follow-up

First Level	0
Second level	1
Abandonment	2

B. Laboratory results recorded at the beginning and end of treatment.

Laboratory tests	**Initial test (values)**	**Final test (values)**
Hematic biometrics		
White series		
Leukocytes		
Neutrophils		
Lymphocytes		
Monocytes		
Eosinophils		
Basophils		
Erythrocytes		
Red series		

Hemoglobin		
Hematocrit		
Medium corpuscular volume		
Medium corpuscular hemoglobin		
Medium haemoglobin concentration		
RDW		
Platelets		
Blood chemistry		
Glucose		
Urea		
Creatinine		
Liver function tests		
Old		
AST		
DHL		
Clotting times		
HO CHI MINH CITY		
TTP		
INR		

C. COVID-19 Symptom Tracking Table

Symptoms	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Headache							
That							
Fever							
Chest pain							
Dyspnea							
Conjunctivitis							
Myalgias							
Arthralgias							
Runny nose							
Odinophagia							
Anosmia							
D. Monitoring table for adverse reactions caused by medicines							
Adverse reactions	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**
Diarrhea							
Nausea							
Vomiting							

Disorientation							
Dizziness							
Asthenia							
Equimosis/petechiae							
Vertigo							
Tinnitus							
Urticaria							
Hemorrhage*							
Angioedema*							
Palpitations*							
Chest pain*							
Other							

*Symptoms considered as criteria for stopping treatment and follow-up, so it will be suggestedto go to second-level hospital.

C. COVID-19 symptom monitoring table *(continued)*

Symptoms	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Headache								
That								
Fever								
Chest pain								
Dyspnea								
Conjunctivitis								
Myalgias								
Arthralgias								
Runny nose								
Odinophagia								
Anosmia								

D. Adverse reaction monitoring table (continued)

Adverse reactions	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Diarrhea								
Nausea								
Vomiting								

Disorientation								
Dizziness								
Asthenia								
Equimosis/petechiae								
Vertigo								
Tinnitus								
Urticaria								
Hemorrhage*								
Angioedema*								
Palpitations*								
Chest pain*								
Other								

*Symptoms considered as criteria for stopping treatment and follow-up, so it will be suggested to go to second-level hospital.

ALARM DATA

Go to the Emergency Department (H.G.Z. 24/ H.G.Z. 48) in the following cases:

Feeling short of air

Chest pain

Confusion

Increased fever

REMEMBER

The follow-up will be carried out specifically by the scheduled video calls, in case of any symptoms of alarm mentioned above go to the emergency rooms of your nearest hospital.

"Predicted modification in patients with COVID-19 under early intervention treatment in U.M.F 13 and U.M.F 20"

Reports:

- Dr. Gilberto Cruz Arteaga. Clinical Coordinator of Health Education and Research. Enrollment 99351417, Family Medicine Unit Enrollment 20. Vallejo 675 Col. Nueva Vallejo, C.P. 07750 Mayor G.A.M., CDMX Tel 55874422 Ext. 15320 and 15368. E-mail: gilberto.cruz@imss.gob.mx

- Dr. Alma Italia Guerrero Martínez, Clinical Coordinator of Health Education and Research. Enrollment 99368649 Family Medicine Unit Enrollment 13-HGO. Woulda Azcapotzalco between Hidalgo and Aztecs C.P.02000 Greater Azcapotzalco CDMx. Tel 55612700 Ext.21315. Email:italia.guerrero@imss.gob.mx

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MEXICAN SOCIAL SECURITY INSTITUTE

U.M.F No.20 / U.M.F. No.13

DOUBTS YOU MAY HAVE DURING THE COURSE OF THE INTERVIEW

DOUBTS DURING THE INTERVIEW

This triptych is in order to clarify some doubts that may arise during the course of the interview when being in treatment.

It is important to note that the interview that is being conducted by videocall, is for the purpose of questioning the symptomatology that is taken during the days that are beingtreated, aimed at improvement or deterioration, or about adverse effects related to the consumption of indicated medicines.

If you have any questions, we suggest that you first read the questions and answers mentioned in this triptych to try to clarify them and not delay the interview time focused on symptoms and adverse effects.

Q&A

1. **Is it possible to get COVID-19 by contact with a person who does not have any symptoms?** Yes, it is possible to get a person who has a mild cough and does not feel sick.

2. **How can we protect ourselves and others if we don't know who is infected?** Practice respiratory and hand hygiene at all times. Keep at least 1.5 m away between you and others, as some infected people may not have symptoms or are mild.

3. **What to do if my family members have been in close contact with me?** Close contact means living with someone who has the disease, or having been less than 1.5 m away from someone who has the disease. If you become ill even with very mild symptoms, such as fever and mild pain, you should isolate yourself at home, if you do not think you have been exposed to COVID-19 but develop these symptoms, isolate yourself and monitor your condition. It is more likely to infect others in the early stages of the disease when you only have mild symptoms.

4. **What does it mean to isolate yourself?** Isolation occurs when a person who has a fever, cough or other symptoms of COVID-19 stays at home and does not go to work, school or public places, It is necessary to use the cover at all times.

5. **Can children and adolescents get COVID-19?** Yes, they have the same chances of becoming infected as any other age group and spreading the disease. However, they are less likely to develop a serious illness.

6. **How to properly use a water cover?**