TITLE:
Study of Immunomodulation using Naltrexone and Ketamine for COVID-19 (SINK COVID-19)

NCT04365985

Approval date: 09/2/2021

Protocol and Statistical Analysis Plan

STUDY OF IMMUNOMODULATION USING NALTREXONE AND KETAMINE FOR COVID-19 (SINK COVID-19)

Investigative Team

Matthew Sims, MD, PhD, FACP, FIDSA (Co-PI): Director Infectious Disease Research, Beaumont Health; Professor of Internal Medicine and Foundational Medical Studies, OUWB School of Medicine

Annas Aljassem, MD, MHSA (Co-PI): Director Functional Pain and Rehabilitation Service, Beaumont Health; Assistant Professor of Physical Medicine and Rehabilitation, OUWB School of Medicine

Levi Hall, PharmD, BCPS: Clinical Pharmacy Specialist – Pain Medicine, Functional Pain and Rehabilitation Service; Assistant Professor of Foundational Medical Studies, OUWB School of Medicine

Carl Lauter, MD, MACP, FIDSA: Section Head Allergy and Immunology, Beaumont Health; Professor of Internal Medicine, OUWB School of Medicine

Research Strategy

1. Significance

1.1 COVID-19: A Major Pandemic Currently Affecting the Entire World

In late 2019 the first cases of what has come to be names COVID-19 were noted in Wuhan China[1]. COVID-19 is caused by a novel coronavirus now designated SARS coronavirus-2 (SARScoV2). As of this writing the most current total worldwide is 336,004 with 14,631 deaths and 98,334 recovered[2]. In the United States there are currently 33,276 cases, 416 deaths, and 178 recovered[2]. In Michigan there are currently 1,037 cases, 9 deaths, and recovered is not currently available[2], the first death in Michigan was reported from Beaumont, Wayne[3]. This certainly represents an underestimate given that testing is still severely limited at this time. The most common presenting symptoms of COVID-19 are fever, cough, and shortness of breath[4] and the disease presentation ranges from asymptomatic to mild to an overwhelming inflammatory response leading to acute respiratory distress syndrome (ARDS) and cytokine release syndrome and ultimately death. The actual mortality of the disease is currently unknown but estimates from China give a mortality rate of 3.6% (95% CI 3.5–3.7)[5]. In the United States mortality estimates to date indicate that fatality was highest in persons aged ≥85, ranging from 10% to 27%, followed by 3% to 11% among persons aged 65–84 years, 1% to 3% among persons aged 55-64 years, <1% among persons aged 20–54 years, and no fatalities among persons aged ≤19 years[6] with an overall mortality rate ~1.5% which varies day to day (0.8%-2.6% depending on the day it is calculated)[7]. Importantly current mortality numbers for the United States are based on a time when the health care system is not overwhelmed. When looking at Italy, a country whose health care system can no longer handle the patient load caused by this disease, the mortality is currently 9.3%[2]. Those at high risk for progression to severe illness include people over the age of 65, people who live in a long term care facility, people with chronic lung disease, people with heart disease, immunocompromised patients, people who are obese (BMI≥40), and people with other chronic medical conditions such as diabetes, renal failure, and liver disease[8]. At Beaumont Health we have noted a trend that severe cases tend to be male, African American, with diabetes and hypertension (unpublished data).

1.2 Treatment of COVID-19

There are no approved treatments for COVID-19. There have been numerous approaches tried and currently at Beaumont Health the standard treatment is hydroxychloroquine and azithromycin based on the study of Gautret et al[9]. Remdesivir is an experimental medication developed for the treatment of Ebola virus and active against RNA viruses which is undergoing clinical trials in COVID[10, 11] and was available for compassionate use but availability is currently on hold due to overwhelming demand while the company organizes an expanded access protocol[12]. Lopinavir-ritonavir is a repurposed HIV protease inhibitor which showed good activity against SARS[13] but has failed to show activity again COVID-19[14]. There are several other compounds in research studies, but this is what is currently available and hospitals are already having difficulty keeping up with the demands for hydroxychloroquine.

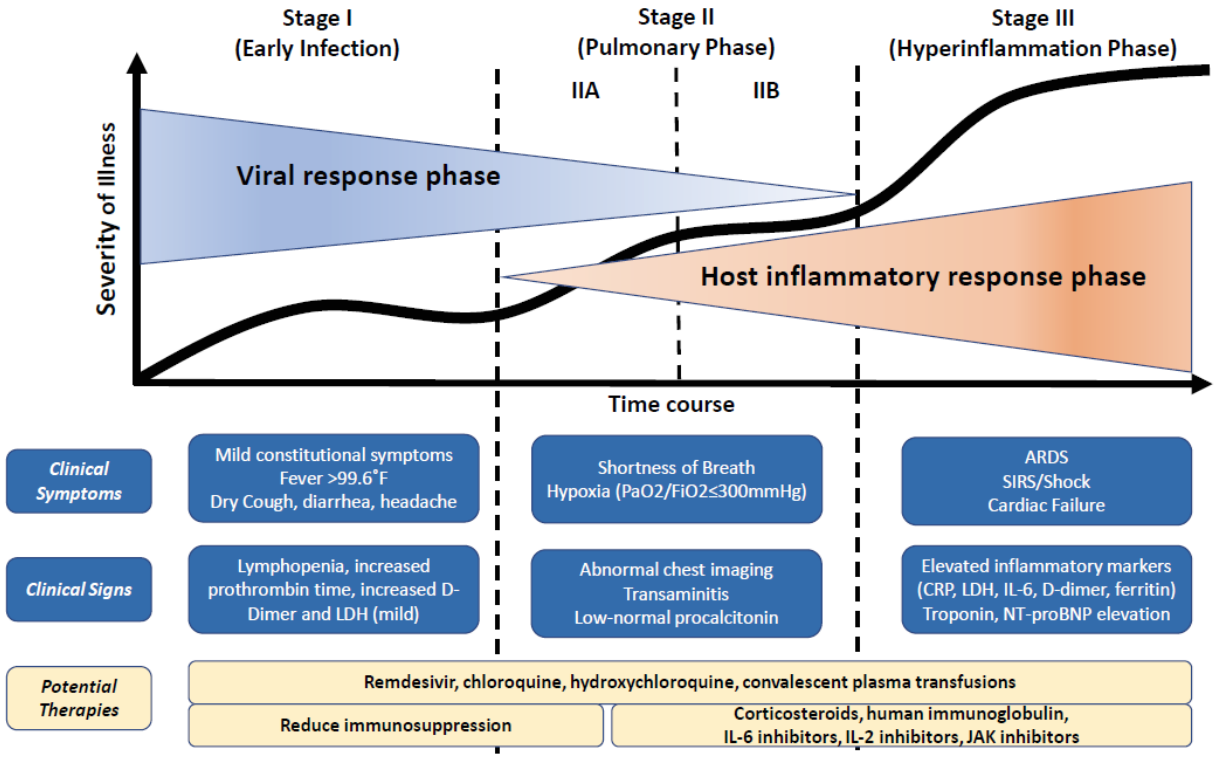
1.3 Immunomodulation as Treatment for COVID-19

One approach for treating severe patients with COVID-19 has been to target the cytokine storm seen in the worst patients is the addition of the immunomodulatory tocilizumab. Tocilizumab is a monoclonal antibody which targets the IL-6 receptor[15]. IL-6 is a cytokine which is one of the main drivers of cytokine storm and tocilizumab has become a standard treatment for the cytokine release syndrome associated with use of CAR-T therapy in cancer[16]. The existence of a hyperinflammatory state and cytokine storm with elevated IL-6, has been reported in severe COVID-19 and were associated with increased mortality in patients in China[17]. A case series of 21 patients treated with tocilizumab between February 5-14, 2020 in China reported great success, including rapid resolution of fever, decreased oxygen requirements, resolution of lung opacities on CT, and reduction of markers of inflammation[18]. Studies of

this compound for COVID in the United States are expected to begin in April and it is currently being used off label for the worst cases but there is limited supply and it is quite costly.

1.4 What We Need in a Treatment for COVID-19

Ideally when you consider the treatment of COVID-19 we need a two-pronged strategy. We need a treatment that will slow or interrupt the progression of the disease from mild/moderate to severe, and we need a treatment to rescue patients who have become severe. COVID-19 infection has three stages and 80% of infected people stay in stage 1 or stage 2A, however 20% of patients progress to stage 2B and of those about 20% progress to stage 3[19].



What is needed is a drug to keep people from progressing into stage 2B or stage 3 and a drug to pull people out of stage 3. The tocilizumab data suggests that interrupting IL-6 is one of the potential pathways to accomplish this.

2. Innovation

2.1 Naltrexone and Ketamine as Immunomodulatory Agents

Low-dose naltrexone has been used off-label for treatment of pain and inflammation in multiple sclerosis, Crohn's disease, fibromyalgia and other pain conditions. Although approved by the FDA as a mu-opioid receptor antagonist for the treatment of opioid and alcohol dependence, it is theorized that lower than standard doses of naltrexone inhibit cellular proliferation of T- and B- cells and block Toll-like receptor 4 (TLR4). It is the blocking of cellular proliferation of T- and B-cells and TLR4 that is thought to provide pain relief and anti-inflammatory benefit. A review article evaluated the evidence of the safety, tolerability and efficacy of low-dose naltrexone for use in chronic pain and inflammatory conditions[20]. Current evidence supports the safety and tolerability of low-dose naltrexone in multiple sclerosis, fibromyalgia, and Crohn's disease. Other studies focus more on subjective measures like quality of life or self-reported pain scores. Studies support a beneficial effect over placebo but evidence for more objective measures is limited.

In a study evaluating low-dose naltrexone (LDN) on the effects of IBD, the authors found LDN induced clinical improvement in 74.5% and remission in 25.5% of patients. Naltrexone improved wound healing and reduced endoplasmic reticulum stress induced by Tunicamycin, lipopolysaccharide or bacteria in the epithelial barriers. Inflamed mucosa samples from IBD patients showed reduced levels of endoplasmic reticulum stress when treated with low-dose naltrexone. The authors concluded that low dose naltrexone is effective and safe and could be considered for treatment of therapy refractory IBD patients[21].

Cant et al concluded that naltrexone has the potential to modulate the secretion of inflammatory cytokines in response to intracellular Toll-like receptor activity. In their study naltrexone inhibited production of IL-6 and TNFα by monocyte, B-cells, and plasmacytoid dendritic cell subsets within the peripheral blood mononuclear cells following treatment with Toll-like receptor (TLR) ligands. This supports the hypothesis that naltrexone has potential use as an immunomodulatory agent[22].

Ketamine has shown in vitro with mice, rats and whole human blood to reduce pro-inflammatory cytokines (IL-6). Elevated levels of IL-6 in the post-operative period were regularly reported to be associated with poor outcome[23-26].

Ketamine shows pleiotropic (showing multiple effects from a single gene) anti-inflammatory effects. Previous researchers have made a strong argument for a very early interaction in the time-course of the inflammatory cascade with ketamine.

The anti-inflammatory effects occur at multiple early steps in the inflammatory process. Central to this argument is nuclear factor NFκ-b, which is an intracellular protein that activates the transcription of genes coding for cytokines (inflammatory mediators). NFκ-b is activated by pro-type inflammatory mediators such as IL-1β and TNFα. Another common pathway is via adenosine receptor systems, such as the Wnt5a-signaling pathway. Ketamine blocks Wnt5a-signaling pathway which is critical for endothelium activation during inflammation[27].

Another study showed patients undergoing cardiac surgery with bypass (procedure known to cause significant inflammation), the administration of a single dose of ketamine 0.25 mg/kg at induction of anesthesia significantly reduced the production of IL-6 (a proinflammatory cytokine). The IL-6 pro-inflammatory cytokine is believed to be significant to the inflammatory process caused by COVID-19. In the same study higher doses of 0.5 mg/kg showed reduce C-reactive protein and IL-10 in addition to the reduced levels of IL-6[28].

Yang et al, showed patients undergoing liver transplantation who received ketamine was associated with reduced levels of circulating TNF-$\alpha$and IL-6[29].

In a meta-analysis by Dale et al six studies consisting of patients undergoing cardiopulmonary bypass operations, abdominal, thoracic and cataract surgeries, concluded that patients receiving IV bolus dose of at least 0.15 mg/kg before surgery significantly inhibits the early postoperative IL-6 inflammatory response[30]. Inana et al demonstrated that ketamine for surgical pre-treatment was at least as important as receiving pre-treatment with methylprednisolone (30 mg/kg) in cardiopulmonary bypass surgery. The study showed the effect of methylprednisolone was short-lived (approximately 1 hour) in comparison with ketamine showing affects lasting up to 6 hours[31].

2.2 A Two-Step Approach to Treatment

Naltrexone at low doses, below the normal therapeutic dose, appears to reduce production of multiple cytokines including IL-6 in a steady pace and is available as an oral preparation. As such it is ideal to use to attempt to modify progression to stage 2B as it can easily be given to both hospitalized patients and patients in the community.

Ketamine at low doses, below the normal anesthetic dose, appears to rapidly reduce the production of cytokines, especially IL-6 and TNFα, for hours after an event which would induce the inflammatory response. This drug is given IV, either by drip or push, and is easily given in a hospital environment and is currently used for opioid sparing therapy. This could not easily be used in the community but could act as a rescue drug in the same way tocilizumab does but with lower cost and easier availability.

2.3 The Benefits and Limits of Naltrexone and Ketamine

Naltrexone is used for alcohol and opioid use disorder at standard doses. Proposed benefit of naltrexone is slowing progression of pro-inflammatory processes. In clinical trials naltrexone is generally well-tolerated. Studies have demonstrated a decreased need for opioid in patients with chronic opioids. Further low dose naltrexone has been shown to decrease inflammatory response, reducing symptom severity in fibromyalgia, Crohn's and chronic regional pain syndrome. This benefit may have a delayed onset or may occur sooner. Naltrexone is not habit forming. If a patient is receiving high dose opioids, low dose naltrexone may precipitate withdrawal symptoms. If side-effects occur, a lower dose of this medication may be used. This agent is inexpensive and readily available in the U.S. market.

Ketamine has been extensively studied in a variety of settings and indications with a well-established side-effect and dosing profile. Ketamine is generally well tolerated and remains inexpensive and widely available on the U.S. market and available for immediate use. With significant percentage of patients receiving chronic opioids or that are opioid-dependent, ketamine would provide the direct benefit of significantly reducing the requirement for opioids or other medications to manage the constellation of pain symptoms patients are experiencing with COVID-19. Proposed benefit of ketamine is to slow or halt progression of pro-inflammatory cytokines (IL-6). A study demonstrated peri-operative use of ketamine reduced inflammation post-operatively.

The short half-life of ketamine minimizes the severity of side-effects, if they occur. Most common adverse effects of ketamine are nausea, increasing blood pressure, worsening baseline psychiatric condition and dissociation. The risk of dissociation is very low due to the dosage used for immunomodulation which is 0.1 to 0.2 mg/kg. Dissociation from ketamine typically occurs at doses greater than 0.5-1 mg/kg.

2.4 A Clinical Trial to Investigate the Use of Naltrexone and Ketamine: Study of Immunomodulation using Naltrexone and Ketamine for COVID-19 (SINK COVID-19)

There is an urgent need to develop new treatments for COVID-19 using easily available and affordable medications. We need to develop a treatment protocol which prevents progression of the disease and a treatment protocol to rescue those with advanced disease. In addition to anti-viral

therapeutics such as discussed above, the addition of immunomodulators to the treatment regimen appear to be an excellent choice for agents which can reduce the pathogenicity of this disease by reducing the dysregulation of autoimmunity which is destructive of normal tissue and when unchecked rapidly leads to mortality. The use of naltrexone will be done in a randomized, double blinded manner whereas the use of ketamine will be unblinded and given as a rescue agent should a patient progress. Additionally should a patient be ineligible for the randomized portion of the study due to already being in stage 2B or stage 3 of the disease, they will be given the opportunity to enter the trial to receive ketamine without being randomized to naltrexone vs placebo.

3. Approach

Specific Aims

Aim 1: Determine whether treatment with low dose naltrexone, 4.5 mg by mouth daily, reduces progression of patients with COVID-19 from stage 1 or stage 2A to stage 2B or stage 3.

1.1: Determine the percentage of patients on naltrexone who proceed to requiring advanced oxygenation (hiflo nasal canula, non-rebreather, CPAP, BIPAP, or intubation)

1.2: Determine the impact of naltrexone on development of renal failure, liver failure, cytokine storm, and ARDS.

1.3: Determine the impact of naltrexone on mortality, length of stay, admission to ICU, length of stay in ICU, intubation, length of intubation, and time till recovery.

Aim 2: Determine if ketamine can improve mortality in patients who progress the need for advanced oxygenation.

2.1: Determine the impact of ketamine on development of renal failure, liver failure, cytokine storm, and ARDS.

2.2: Determine the impact of ketamine on mortality, length of stay, admission to ICU, length of stay in ICU, intubation, length of intubation, and time till recovery.

3.1 Research Design

To date we have over 100 patients admitted to Beaumont, Royal Oak in the space of 1 week with about 25% needing to be admitted to the ICU. Of the first 101 patients admitted 25 ended up admitted to the ICU, 12 to the advanced COVID Unit (medical progressive care), and 64 to COVID general floor, these numbers can fluctuate and those in the COVID units can still progress to the floors. Approximately 70 of the 101 patients were treated with hydroxychloroquine and azithromycin.

This is a prospective, single center, randomized, double blinded study of naltrexone for the treatment of COVID-19 with an open label extension using ketamine as a rescue drug for patients who progress in their disease. We plan to recruit up to 500 patients. All COVID positive patients will be screened by the following criteria:

Inclusion	Exclusion
Positive for COVID -19	Known allergy to naltrexone
Admitted to Royal Oak	Known allergy to ketamine
Age ≥18	Diagnosis of schizophrenia or acute psychosis
On ≤6L Oxygen by nasal cannula [A]	Pregnancy
	On chronic high dose opioids > 90mg morphine mg equivalence
	Use of naltrexone or Vivitrol within 90 days

A – If on more than 6L oxygen by NC patient can be enrolled as a non-randomized patient directly into the ketamine rescue group.

If eligible the patient or their LAR will be approached for inclusion in the study. Given the nature of the pandemic and the shortage of personal protective equipment all consenting will take place over the phone in the presence of a witness as per IRB emergency safety policy during COVID19.

Patients who consent will be randomized to one of 2 arms: Arm 1 – low dose naltrexone 4.5 mg by mouth per day (can be given via NG tube if needed). Arm 2 – placebo by mouth per day. Treatment will be for 30 days past discharge. If the patient develops severe insomnia or shows symptoms of opioid withdrawal the dose of naltrexone can be decreased to 3 mg by mouth per day. If the patient continues to demonstrate issues on the 3 mg reduced dose of naltrexone the dose can be further reduced to 1.5 mg by mouth per day or held temporarily if needed. Reasons it may need to be held include if it is interfering with sedation, due to the unique issues with sedation in COVID-19 often requiring large amounts of opioids. Even low dose naltrexone seems to interfere with sedation in some of the patients. Since opioids, particularly fentanyl, are stored in fat, a patient who is starting on study who has been on opioid based sedation for 3 days or more can be started on a reduced dose of naltrexone (as above) or the naltrexone can be held from start and only ketamine used until their sedation is weaned to levels where clinically is it felt the naltrexone will no longer cause issues with sedation or signs of withdrawal. A patient should have naltrexone started by the time ketamine is no longer needed.

Imaging data, flowsheets, and medical notes will be abstracted to generate a daily summary of the patient's status to determine renal failure, liver failure, cytokine storm, ARDS, improvement vs progression of disease, need for advanced oxygenation, ICU status, and mortality.

If at any point a patient requires advanced oxygenation (hiflo nasal cannula, non-rebreather, CPAP, BIPAP, or intubation) for more than 15 minutes they will then be given ketamine as a rescue treatment and remain on the Naltrexone or placebo. Ketamine will initially be given at a dose of 0.15 mg/kg based on total body weight (max 20 mg) every 6 hours (+/- 1 hour) by intravenous piggyback over 30 minutes. Ketamine will continue until the patient is deemed stable for low level oxygen. If the patient relapses after the ketamine is stopped they can be restarted on the ketamine. If the patient continues to worsen or displays evidence of cytokine storm (elevated markers of inflammation, evidence of ARDS, continuous fever) the dose of ketamine will be increased to 0.3 mg/kg IV every 6 hours (max 30 mg). The dose of ketamine can be reduced back to 0.15 mg/kg at the clinical decision of the physician investigators. If a patient has issues with hypertensive emergency the dose of ketamine can be held until the hypertensive emergency is controlled.

In addition, a patient can receive ketamine if they are not yet on advanced oxygenation if the investigating physician feels they are moving toward cytokine storm based on the markers of inflammation and clinical factors such as worsening imaging and unrelenting fever.
If a patient transitions to comfort care the patient will remain in the study for data collection purposes. Study medications may be held if requested by the clinical team, patient, LAR or family.

Patients who at screening are already requiring advanced oxygen can be consented and enrolled in the study and immediately will skip the randomization and be placed on naltrexone and receive ketamine as the starting treatment in an open label manner.

All patients will have the following labs drawn on a daily basis for the first 5 days after randomization and then weekly while in the hospital: IL-6, CBC with differential, CMP, Triglycerides, Ferritin, Fibrinogen, ESR, CRP, LDH, CK, Troponin, and D-dimer. An additional IL-6 will be drawn prior to the first dose of study drug to establish a baseline. In addition if a patient is placed on ketamine these labs will be drawn for the 5 days following initiation of ketamine and then return to once a week. These labs are measures of general medical status, renal status, liver status, and markers of inflammation. The use of these labs is 2 fold, they may be used up front to help determine when I patient should have the dose of ketamine escalated and they will be reviewed retrospectively for the research to determine impact of

the study drugs. IL-6 in particular will only be looked at retrospectively as it is a send out test and the length of time to get results is 3-5 days. Each patient will have the following vital signs from the prior calendar day and related data recorded on a daily basis: maximum temperature, minimum temperature, maximum heart rate, minimum heart rate, maximum blood pressure (based on mean arterial pressure), minimum blood pressure (based on mean arterial pressure), maximum oxygen patient is on and the method of delivery, minimum oxygen patient is on and the method of delivery, maximum respiratory rate, minimum respiratory rate. The nurses and physicians participating in this study will also be looking for progression of oxygen requirements whenever they access the chart and the floor staff will be instructed to call the study team immediately for consideration of ketamine rescue.

After the first five days the labs will be collected once a week (every 7 days +/-1 day) until discharge. Any of these labs drawn by the treatment team will be collected if they match the timeframe of the study labs additional labs will not need to be ordered for the study.

For all patients we will collect medical history specifically including what COVID-19 symptoms were present and for how long, the date and time of the positive COVID test and what lab it was run at, demographics, concomitant medications on a daily basis, and any available cardiac markers including CK, troponin, myoglobin and echocardiography results.

After discharge patients will be called once a week (+/- 3 days) for 1 month to determine their current health status and review their medication compliance. If at the 1 month mark the patient has not resolved their symptoms fully the calls will be extended for an additional month, once a week.

While the exact time the patient will remain in the study is unclear depending on duration of the admission and duration of symptoms, we expect it will be approximately 3 months on average.

3.2 Measurements of Outcomes

Primary Outcome Measure:
1. Progression of oxygenation needs
Count of participants initially presenting with mild/moderate disease who progress to requiring advanced oxygenation (high flow nasal canula, non-rebreather, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), or intubation)
[Time Frame: up to 1 month]

Secondary Outcome Measure:
2. Renal failure
Count of participants who develop or experience worsened renal failure as defined by RIFLE criteria, a 5-point scale where the categories are labeled: Risk-Injury-Failure-Loss-End stage renal disease, with Risk being the least severe and End stage renal disease being the most severe. The criteria for determination of stage are factors of serum creatinine and urine output. Numbers of participants worsening one or more RIFLE stages will be reported.
[Time Frame: up to 1 month]
3. Liver failure
Count of participants who develop or experience worsened liver failure as defined by serum transaminases five times normal limits

[Time Frame: Daily times 5, then weekly]

4. Cytokine Storm
Count of participants who develop cytokine storm as measured by elevated markers of inflammation (elevated D-dimer, hypofibrinogenemia, hyperferritinemia), evidence of acute respiratory distress syndrome (ARDS) measured by imaging findings and mechanical ventilator requirements, and/or continuous fever (≥ 38.1 ° Celsius unremitting)
[Time Frame: 1 month]

5. Mortality
Count of participants who die from COVID-19
[Time Frame: up to 1 month post hospital discharge]

6. Length of hospital stay
Length of hospital stay in days
[Time Frame: 1 month]

7. Intensive Care Unit (ICU) admission
Count of patients admitted to the ICU at any time during index hospitalization
[Time Frame: 1 month]

8. Intensive Care Unit (ICU) duration
Length of ICU stay in days
[Time Frame: 1 month]

9. Intubation
Count of participants requiring intubation
[Time Frame: 1 month]

10. Intubation duration
Length of intubation, measured in days
[Time Frame: 1 month]

11. Time until recovery
Time measured in days from hospital admission to determination patient is stable for discharge
[Time Frame: 1 month post hospital discharge.]

3.2 Statistical Analysis

Descriptive statistics will be provided for all variables collected including patient demographics, numbers progressing to requiring more oxygen, and all secondary outcomes. Categorical variables will be summarized as counts and percentages. All continuous variables will be summarized as means+/- the standard deviation where normal or median and 25th, 75th percentiles if not normal. The minimum and maximum will also be provided.

Analysis Sets: Data analysis will be performed on a full analysis set (FAS), a per protocol set (PPS), an intent-to-treat (ITT) set, and a safety analysis (SA) set.

The FAS will be used for the primary analysis. The FAS will consist of all randomized subjects who receive at least one naltrexone/placebo treatment. All analyses using the FAS will group participants according to randomized treatment in an intent-to-treat analysis.

The PPS will be used for a supportive analysis and will be defined as all subjects included in the FAS who do not have any significant protocol deviations. All analyses using the PPS will group subjects according to treatment the subject actually received.

The safety data set will include all subjects with all safety data but will lack any outcome data. This data set will be used for reporting to the internal safety committee.

Missing Data: We will evaluate the potential impact of any missing data on analyses before deciding how to include missing data. Missing data will not be replaced by substitutions or imputation as long as the percent missing for any of the variables is less than 5%. Should the percent missing increase above 5%, we will use multiple imputation to replace missing data and conduct any analyses outlined below.

Primary Outcome: Progression to requiring more oxygen will be the primary outcome, and we will compare the percent patients progressing between the two arms of this study. The primary hypothesis is that the percent progressing for those in the naltrexone arm will be less than the percent progressing in the placebo arm. We will use the Pearson chi-squared test this hypothesis using a one-sided type 1 error rate of 0.05. We will also estimate the difference in proportion progressing using a Bayesian approach with independent Jeffrey's priors for both groups and numerical integration to obtain the credibility interval for the difference in proportions.

Sample Size Determination: We assumed that 20% of patients admitted to the hospital will show progression to requiring more oxygen, and that we want to detect if naltrexone reduces the progression rate to no more than 10%. With these assumptions, a sample size of 154 per arm (308 total) is required to have 80% power based on a two-sample t-test, using PASS 16.

Secondary Outcomes: To examine the potential impact of ketamine on mortality, we will use the chi-squared test to evaluate the hypothesis that mortality is reduced in the naltrexone arm. We will also estimate the difference in proportions using the Bayesian approach noted above. We will use a type 1 error rate of 0.05 for this secondary outcome.

For all remaining secondary outcomes, we will estimate the difference between the two arms and not test for differences between the two arms since these data will be used in planning future studies. For dichotomous outcomes (renal failure, liver failure, cytokine storm, and ARDS), we will use the Bayesian approach discussed for estimating the difference in proportions. We will use generalized linear models to estimate the difference in durations (number of days in ICU, number of days on a ventilator, and length of stay), evaluating the distribution to use based on the data. We will consider using the Poisson, negative-binomial, and normal distributions. We will use a Bayesian approach, using a flat prior on the difference in means parameter. We will calculate 99% credibility intervals for all of these secondary outcomes given the multiple outcomes being examined.

For statistical analysis the biostatisticians and Data analytics teams at Beaumont (Rob Podolsky and Shirley Qu) will pull patients who were not on SINK, had COVID-19 with as close to a direct match to patients with similar profiles who were treated on the SINK study. The match to the patients on SINK will aim to compare the outcomes of the two groups, to see if there is a difference in the outcomes. The evaluation is a chart analysist aimed at focusing on the outcomes of the study.

Safety Measures:

There will a full DSMB consisting of an infectious disease physician, two additional physicians, a biostatistician, and a pharmacist. A medical monitor will review safety data weekly (+/- 7 days). Adverse event summaries will be emailed to the committee weekly. The DSMB will meet monthly but can choose to modify that schedule based on patient recruitment levels. At a minimum they will have quarterly meetings no matter what the level of recruitment is. When 20 patients (from the open-label arm) have been placed on ketamine enrollment will be held. The DSMB will review the data for safety of using ketamine. The DSMB will then present their findings to the IRB to determine if protocol revisions are necessary and when enrollment may resume.

With the completion of the initial safety review, going forward the DSMB will formally meet at least each quarter with the option to meet earlier if enrollment is found to be high enough to warrant it. There are no further automatic holds to enrollment. PI and study team will monitor study patients at least daily or more frequently due to their severe illness risks.

4. Future Directions

If the **SINK COVID-19** study is successful we plan to develop a large multi-center trial to confirm the results on a larger scale.

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