Stellate Ganglion Blockade in COVID-19 Positive Patients

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STELLATE GANGLION BLOCKAGE IN COVID-19 POSITIVE PATIENTS
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Brief Summary:
The proposed research plan will reflect the proof of concept of our modified stellate ganglion block in the human subject, following several key cardiac and pulmonary parameters leading to clinical benefit as well as the safety aspects of stellate ganglion blockade (SGB). Enrolling subjects will be enrolled from patients cared for in the COVID ICU/progressive care at Nebraska Medicine.
Patient eligibility will be determined based on the following criteria; Any patient between the ages of 40-75 with laboratory established COVID-19 infection (via rRT-PCR) requiring critical care in an intensive care unit, signs or symptoms consistent with ARDS, at least 2 of the following (respiratory rate ≥30 breaths per min, oxygen saturation at rest ≤ 93%, PaO2/FIO2 ≤ 200 mm Hg, bilateral infiltrates on chest radiograph or CT not due to cardiac failure, requiring non-invasive or invasive mechanical ventilation.) Block randomization will be used to determine equal allocation to control (labs, nitric oxide levels +SOC) and intervention group (labs, nitric oxide levels, SGB procedure, perineural catheter 5 days). Once enrollment criteria are met, baseline assessments will be completed by the Acute Pain Service (APS). They will place SGB and manage intervention group for 5 days. Data collection will be collected through Day 5 of hospital stay, discharge information will be documented, and survival at 90 days via telephone to complete SF 36 questionnaire.

Section 1.0 Objectives:

To assess the safety, tolerance, oxygenation, lung and cardiac function, proinflammatory immune response and nitric oxide changes associated with the use of our modified SGB protocol in patients with ARDS due to COVID-19 disease.

Secondary (to be confirmed at later trial phase): To determine the association of use of our modified SGB protocol in patients with ARDS due to COVID-19 disease on: incidence of cardiac arrhythmias associated with ARDS, need and duration of use of mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

Section 2.0 Introduction:

The novel coronavirus, now officially designated as severe acute respiratory syndrome coronavirus-2 or SARS-CoV-2 was first identified in Wuhan, Hubei Province, China in December of 2019. Since its identification, Coronavirus disease 2019 (COVID-19) has evolved into an international public health emergency. As is common for the coronavirus family, (SARS-CoV-1 and MERS), COVID-19 is associated with acute respiratory infection. The mortality of COVID-19 infection is mostly due to complications related to pneumonia and ARDS [1].
Strategies to mitigate ARDS and consequent multi-organ failure is in high demand. Currently, there are no FDA-approved treatments outside of supportive care for patients suffering from ARDS due to COVID-19. Unique to COVID-19 associated respiratory failure and ARDS is the early overproduction of proinflammatory cytokines. This exaggerated immune response or "cytokine storm," is felt to lead to increased vascular hyperpermeability, multiorgan failure, and death. Many ARDS/lung injury patients manifest refractory hypoxia, cardiac arrhythmias and acute myocardial damage[10-13]. Cardiovascular complications such as circulatory failure are

frequently associated with COVID-19 ARDS and are associated with a poor outcome[14]. Case series have noted cardiac arrhythmias, cardiomyopathy, and cardiac arrest as terminal events in Covid-19[15-17]. Stellate ganglia block (SGB) is a common clinical intervention to treat both sympathetic nervous system overstimulation and refractory cardiac arrhythmia. Traditional chemo-neuromodulation paradigms employ a single SGB strategy deriving short-term (lasting a few hours to one day) control of sympathetically mediated symptoms, e.g., cardiac arrhythmias are controlled by temporarily blocking stellate neuronal activity with local anesthetics[18-20]. Once the anesthetic effect is withdrawn, cardiac arrhythmias recur. We propose a modified SGB strategy utilizing a continuous infusion of medications instead of a bolus injection. We expect to achieve a lasting chemo-neuromodulating effect in COVID-19 ARDS patients reducing overall inflammation, improving pulmonary function, and reducing cardiac complications.

Preliminary Data: A notable innovation of our modified SGB approach is the addition of clonidine and dexamethasone to a local anesthetic (LA). The scientific rationale supporting this modification is derived from both the literature as well as work done here at UNMC by Dr. Hanjun Wang (Figure 1).

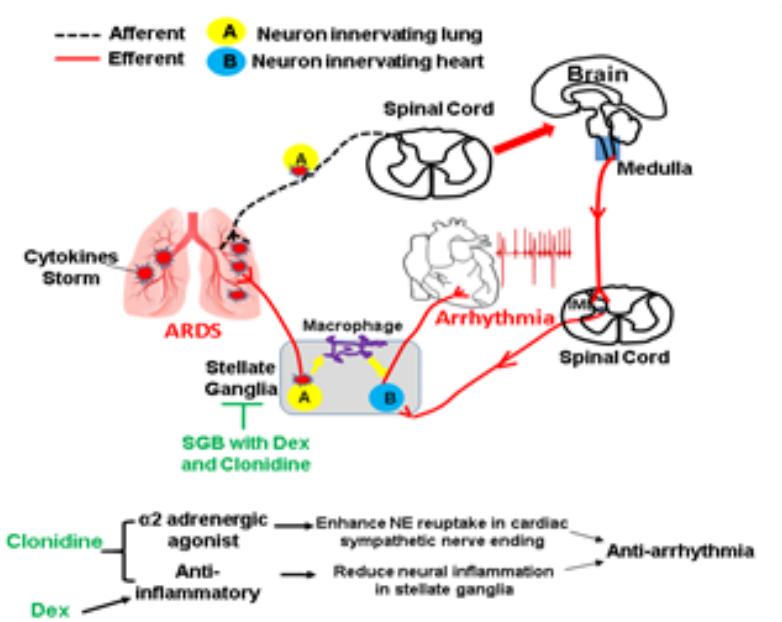


Figure 1. A schematic of our hypothesis indicating how SGB with clonidine and dexamethasone (Dex) could have a beneficial effect on arrhythmia and cardiac complication in acute respiratory distress syndrome (ARDS).

Recent animal studies from Dr. Wang's lab suggest macrophage activation in stellate ganglia plays a critical role in mediating acute lung injury-caused cardiac arrhythmia (Figure 2).

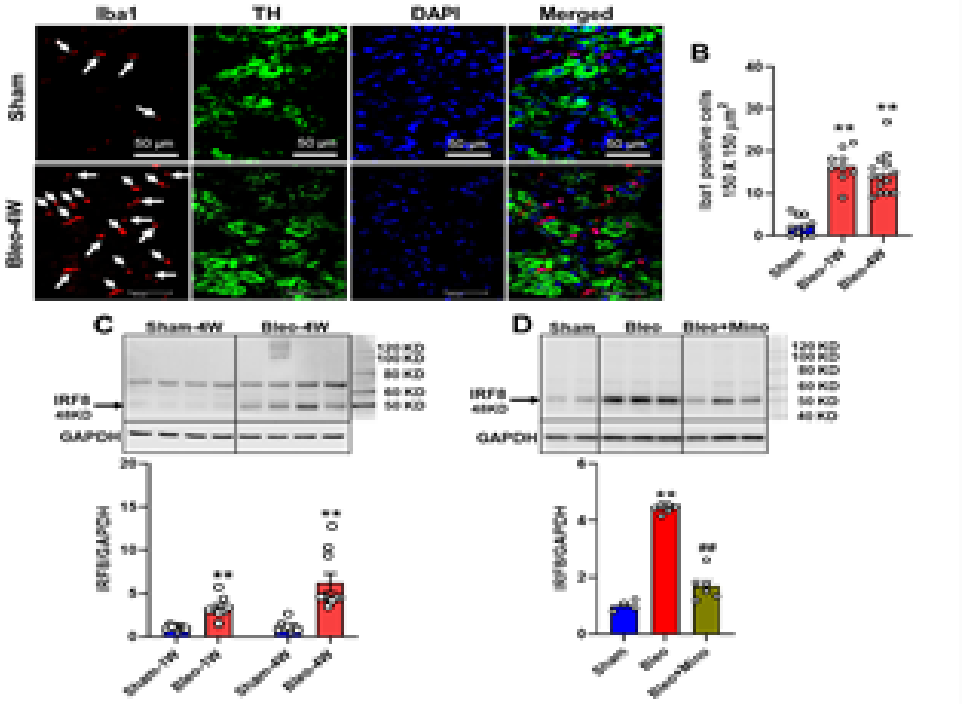


Figure 2. Representative immunofluorescence images (A) and summary data (B) showing increased number of Iba1-positive macrophages in the stellate ganglia (SG) in bleo-treated lung injury rats. TH, tyrosine hydroxylase, a SG neuron marker; DAPI, a nuclear marker. C, representative western blot images and mean data showing that IRF8 (a macrophage activation marker) expression was time-dependently increased in the SGs of 1-week and 4-week Bleo rats. (D), representative western blot images and mean data showing that the increased protein expression of IRF8 in the SGs of 4-week Bleo rats was largely prevented by minocycline (Mino).

Additionally, systemic administration of an anti-inflammatory medicine, minocycline, can largely block macrophage activation and arrhythmias in a bleomycin-induced lung injury rat model (Figure 3).

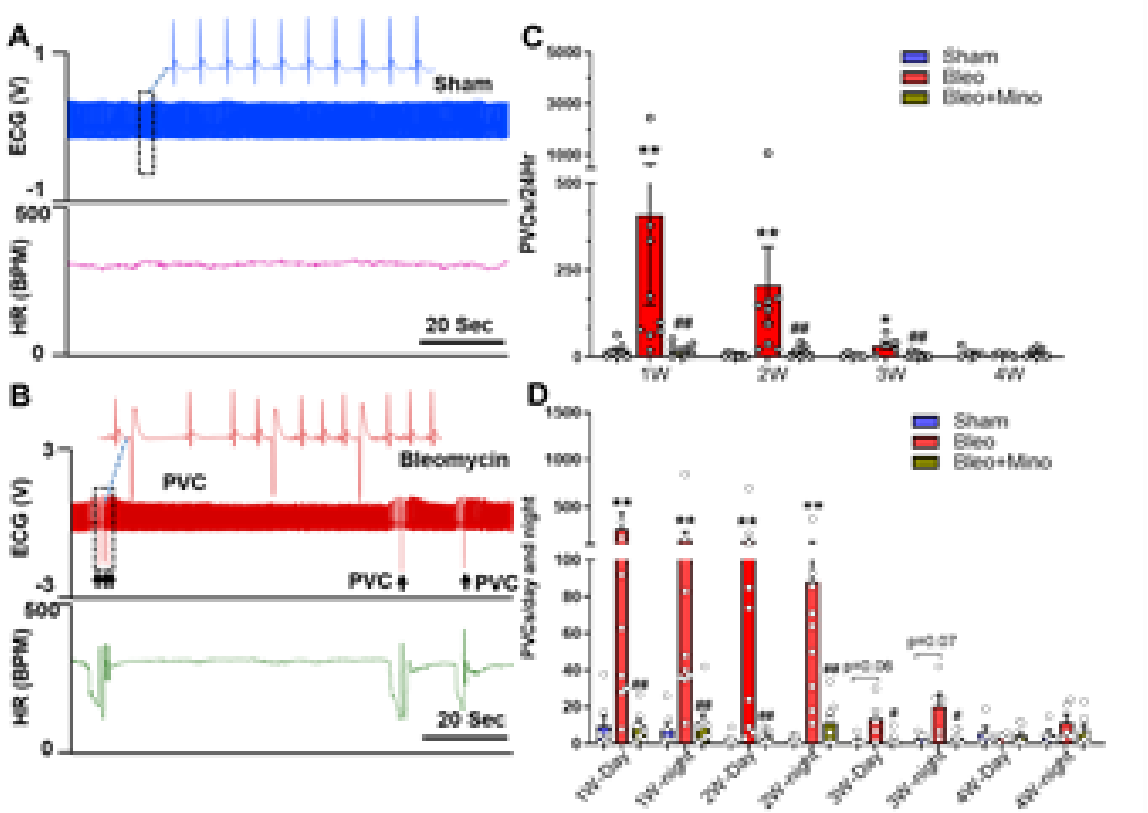


Figure 3. Original tracing (A and B) and mean data (C and D) showing the number of PVCs per 24 hours and their distributions over day and night in sham, Bleo, and Bleo+Mino rats at different time points (1w, 2w, 3w and 4w post Bleo). Data are expressed as mean±SE. n=5-9/each group. **P<0.01 vs. sham group, #P<0.05 and ##P<0.01 vs. Bleo group.

Dr. Wang's findings support the novel concept that local delivery of anti-inflammatory/anti-macrophage medicine to/around the stellate ganglia may be a promising new therapy for treatment of inflammation-augmented comorbidities (especially cardiac) in acute lung injury/ARDS patients. To test this hypothesis in humans, we propose addition of two medications to the LA-SGB. Low dose dexamethasone will be added to ameliorate stellate ganglia inflammation directly. Additionally, based on Dr. Wang's work, we will also add clonidine. This additive is supported in that 1) clonidine selectively stimulates α2 adrenergic receptor and promotes the norepinephrine reuptake by cardiac sympathetic nerve endings [20-22]) clonidine has local anti-inflammatory effects via promoting apoptosis of leukocytes and switching pro-inflammatory macrophage to anti-inflammatory macrophage[23]. In addition to testing, the beneficial cardiac effects of our modified SGB approach, we also aim to examine if SGB could also improve lung damage/inflammation as well as respiratory function in COVID 19 patients. This work is also previously performed in animal models. In septic rats,

SGB was able to attenuate sepsis related lung injury and decrease serum levels of TNF-alpha and IL-6[3]. In a direct lung injury model using rabbits, SGB showed decreased levels of TNF-alpha, IL-6 and IL-10 as well as decreased postmortem acute lung injury[4]. Human studies in trauma patients revealed immunological findings of decreased pro inflammatory cytokine production, and no negative effect on cardiovascular or pulmonary parameters.[2] Finally, in one small human study of patients undergoing one-lung ventilation, SGB was shown associated with increased plasma levels of nitric oxide and improved oxygenation[5]. In animal models, SGB was shown to improve pulmonary hypertension via NO production; oxygenation was improved as well.[6-7] Several studies show nitric oxide can directly inhibit RNA synthesis, viral protein accumulation and virus released from infected cells. This was found in a variety of viruses, but specifically SARS. Not only was replication of the virus reduced, by NO was found to block SARS binding to the receptor host.[8-9] We expect that the modified SGB strategy will achieve prolonged anti-arrhythmia and anti-inflammatory effects in COVID patients.

Study Rationale:

Available research indicates that an exaggerated immune response plays a key role in the cardiopulmonary pathophysiology of COVID-19. Preliminary data from previous studies at UNMC suggest that acute lung injury initiates robust and sustained macrophage activation in thoracic dorsal root ganglia and in stellate ganglia, resulting in increased cardiac and pulmonary afferent and efferent neuronal sensitivity. In the current proposal, we plan to validate a novel therapeutic strategy to treat coronavirus-induced cardiopulmonary symptoms and complications by local delivery of bupivacaine, dexamethasone, and clonidine to the stellate ganglia. Single injection and continuous infusion SGB have been safely utilized clinically and in many human studies.

Section 3.0 Eligibility Criteria:

Inclusion:

- Subject admitted to COVID ICU/progressive care, age 40-75 years old

Subjects must have + covid test with signs of impending respiratory compromise as identified by having at least 2 of the following:

- Respiratory rate ≥30 breaths per min
- Oxygen saturation at rest ≤ 93%
- PaO2/FIO2 ≤ 200 mm Hg
- bilateral infiltrates on chest radiograph or CT not due to cardiac failure
- Requiring non-invasive or invasive mechanical ventilation.

Any patient with a + covid test and any cardiac tachydysrhythmia (excluding sinus tachycardia) will be included regardless of respiratory status. (Note: The broader inclusion of patients who have cardiac tachydysrhythmia is based on our prior experience and other reported beneficial antiarrhythmic effects of SGB in this patient group.)

Exclusion:

- Hemodynamic instability (>2 vasopressors)
- Heart rate < 60 beats per minute
- Systolic Blood pressure of less than 80 mmHg
- pre-hospital diagnosis of heart failure or fluid overload
- anatomical inability to perform block
- prior sympathectomy
- Patient currently enrolled in another clinical trial for COVID-19 or respiratory distress/ARDs
- Uncorrectable coagulopathy
- ECMO already engaged
- On Nitric Oxide
- Pre-existing multi-organ failure (>2 organ systems)
- Allergic to dexamethasone, clonidine, or bupivacaine.
- If female, currently pregnant or breast-feeding.
- Investigators determine the subject would be too unstable to participate in the study intervention.

If a woman of childbearing age is enrolled as a subject and there has not been a pregnancy test during their current inpatient stay, a urine or blood pregnancy test will be performed. Pregnancy will not be allowed for this study as the drug is absorbed systemically and there are known risks to the fetus.

Section 4.0 Registration Procedure:

A prospective block randomized phase I/II two arm unblinded trial of a modified SGB protocol incorporated into Standard of Care vs UNMC standard of care Only for ARDS COVID-19 patients.

Subjects and/or Legally Authorize Representative (LAR) will be approached while subject is in the ICU/progressive care. If subject is unable to participate in the consenting process, the LAR will be contact via telephone and/or video chat. Consents will be sent to LAR electronically. PI and/or Sub-I will be present for all consenting process regardless is the ICF process takes place in person or video digital presence.

The randomization will be done by using *Stratified Permuted Block Randomization* in which sequential trial participants will be subdivided into the strata as indicated by their age-groups ie; 40-59, 60-74, 75-85 years and thereafter allocated to study group via block randomization within the strata so that the balance between age groups between the two study groups stays close to equal throughout the trial.

Section 5.0 Treatment Plan of Research Design:

A prospective block randomized phase I/II two arm unblinded trial of a modified SGB protocol incorporated into Standard of Care vs UNMC standard of care Only for ARDS COVID-19 patients.

Sixteen subjects will be enrolled. Eight in the control arm and eight in the intervention SGB arm.

Subjects will be identified on the COVID unit. The study will be explained to the subject and if the subject wishes to voluntarily participate, the ICF will be signed. If the subject is unable to sign consent, the LAR consent will be utilized. If LAR is not present, an electronic link to the consent will be sent to the LAR via email.

The attending proceduralist will perform the SGB in the ICU/progressive care. ICU/progressive care nurse will provide patient monitoring and assistance during the procedure. Standard monitors and ACLS resuscitative equipment will be immediately available. A norepinephrine solution will be at bedside to treat potential hypotension associated with SGB. The SGB perineural catheter will be placed using standard sterile technique. Initial perineural bolus injection - clonidine 100 mcg, Decadron PF 5mg, and 0.25% bupivacaine 5 ml is delivered. A Cadd perineural infusion 0.2% bupivacaine will be initiated at 2ml/hr for 5 days. Acute pain service will discontinue infusion and remove the catheter after 5 days.

All adverse events and serious adverse events related to the SGB. All other adverse and serious adverse events, including death will be reported per IRB requirements. Laboratory analysis will be obtained at baseline (prior to block, baseline) and on day 1, day 3, and day 5. Labs include a cytokine panel (TNF-beta, IL-6, and IL-1β), measurements of exhaled nitric oxide levels, and CRP (daily). Vital Parameter Analysis: Oxygenation, supplemental oxygen, type of respiratory support and need for mechanical ventilation, blood pressure i.e. hypotension requiring vasopressors and utilization of ECMO, heart rate, heart rhythm/new dysrhythmias, ICU/progressive care length of stay and discharge disposition will be collected from the EMR.

Control group: There will be no sham procedure for the control group. The control group will have nitric oxide levels performed once a day by a member of the research team. Lab draws will be drawn at the same frequency as the treatment group.

Treatment group:
The treatment group will have a SGB placed by the APS.

Appendix A. Protocol for stellate ganglion blockade in COVID-19 patients.

ICU/progressive care RN will follow Med-27 NM policy for peripheral nerve catheter management. APS will utilize a similarly established standard of care in managing the catheters daily, for 5 consecutive days. This includes daily rounding on the patient to assess for signs of infection, muscle weakness, voice hoarseness, hematoma, intravascular migration, local anesthetic systemic toxicity, correct medication verification, verification of pump setting, evaluation for Horner's syndrome (expected), patient education, and proper dressing coverage.

Horner's syndrome refers to a constellation of symptoms that are associated with a stellate ganglion block. These include a decreased pupil size on the affected side, delayed reaction to light on the affected side, drooping eyelid and decreased sweating on the affected side. Increased temperature and vascular dilation are also noted on the affected side with stellate ganglion block.

Schedule of events: *treatment group only

Assessment	Screening: Visit-1	Baseline, Enrollment, Randomization : (Day 0)	Treatment Day 1	Treatment Day 2	Treatment Day 3	Treatment Day 4	Treatment Day 5	EOS Discharge from hospital	Follow-up: Day 90
Inclusion/Exclusion Criteria	X								
Informed Consent Form	X								
Enrollment/Randomization	X								
Demographics	X								
Eligibility	X								
Medical History	X								
Data Collection (Vitals ect)	X	X	X	X	X	X	X	X	
Acute Pain Service		X*	X*	X*	X*	X*	X*		
Stellate Ganglion Block		X*							
CRP		X	X	X	X	X	X		
TNF-Alpha		X	X		X		X		
IL-Beta		X	X		X		X		
IL-6		X	X		X		X		
Nitric Oxide Level		X	X	X	X	X	X		
Telephone Call									X
Concomitant Medications		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X

Section 6.0 Measurement of Effect:

We will be taking *measurement of the biomarkers indicative of oxygenation, lung and proinflammatory immune response and nitric oxide* - specifically,

a) differences in mean/median values for SGB vs SOC will be assessed at each of the study designated time points for all the continuous biomarker measures - by assessing magnitude of difference and its 95% confidence level and testing differences for statistical significance at each of the time points;

b) Differences in mean/median values for SGB vs SOC will be assessed at treatment day 5 - adjusted for baseline levels

c) Differences in changes from baseline levels for SGB vs SOC as measured by comparison in slope trends;

d) Differences in frequency of adverse events for SGB vs SOC over the study period from treatment through 90 day of follow up;

Secondarily,

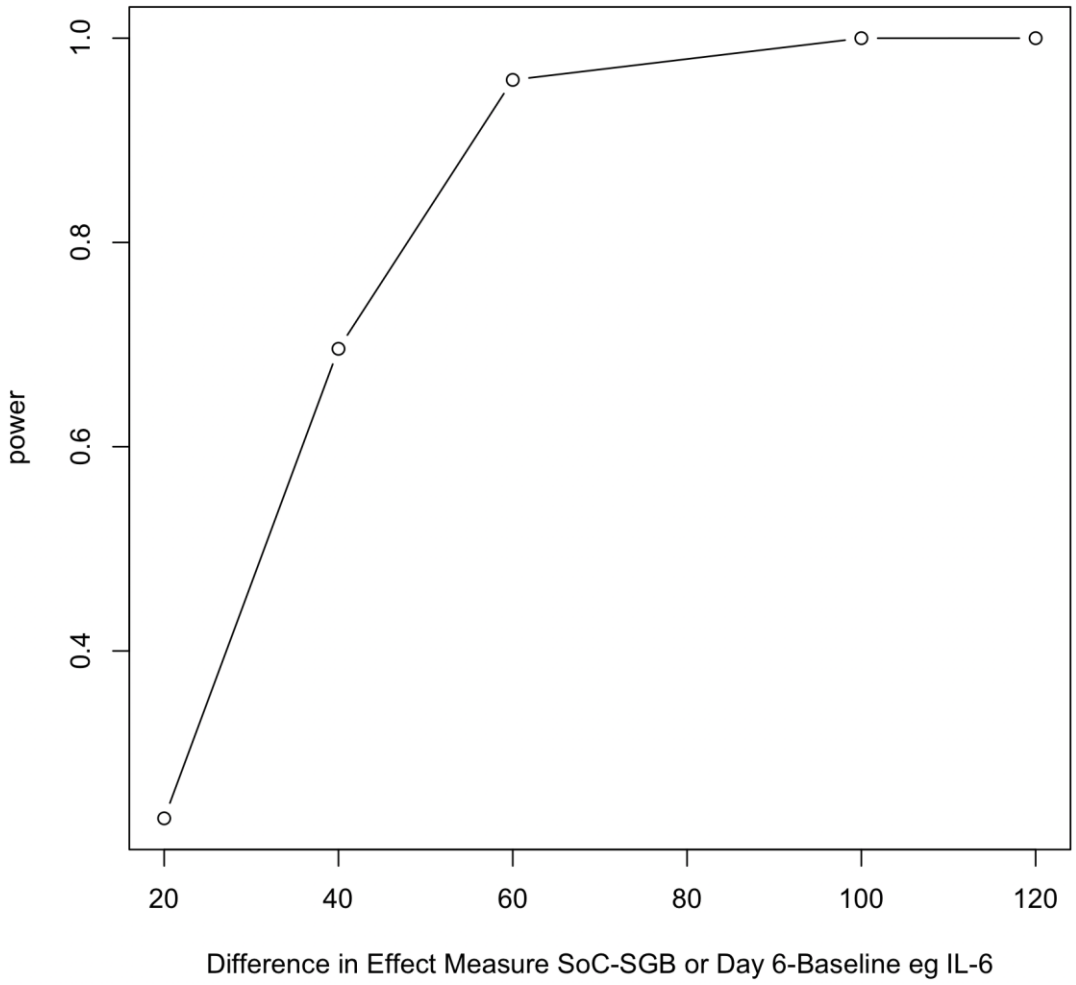
e) Differences between SGB vs SOC in *frequency* and *time to occurrence* of *cardiac arrhythmias*;

f) Differences between SGB vs SOC in frequency of *need for* and *duration* of use *mechanical ventilation* and/or *extracorporeal membrane oxygenation (ECMO)*;

g) Differences between SGB vs SOC in survival experience over treatment period through 90 -day discharge follow up

Sample Size issues:

For power computations we assume that SGB will particularly have an impact in reduction of inflammatory response as measured by IL-6. Looking at a meta-analyses of IL-6 values [Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect. 2020;50:382–383. doi: 10.1016/j.medmal.2020.04.002. 2020/04/08] and picking the largest of studies of COVID patients [Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020, http://dx.doi.org/10.1093/cid/ciaa248 [pii: ciaa248].], we estimate the overall mean (SD) IL-6 for COVID-19 patients to be 21 pg/mL (30.1). Using these estimates we see that a sample of 16 patients equally randomized into SGB (n=8) and SoC (n=8) would provide sufficient power to observe magnitude of differences in mean of IL-6 from as small as about 50 pg/mL and larger with 80% power at the 5% significance level assuming 2-sided hypothesis testing. (see Power Figure). The study [Liu MH, Tian J, Su YP, Wang T, Xiang Q, Wen L. Cervical sympathetic block regulates early systemic inflammatory response in severe trauma patients. Med Sci Monitor. 2013;19:194–201.], indicates that SGB is capable of eliciting reductions of IL-6 between groups and from baseline of magnitudes of greater than 100 pg/mL within 72hrs of first injection.



Section 7.0 Study Parameters:

Baseline Assessments

- Current Fio2/PaO2 ratio
- Current type of ventilation and oxygen use
- Current production of nitric oxide via Niox
- Current blood pressure and heart rate parameters
- Labs: IL-1beta, TNF-alpha, IL-6, ABG, CRP
- Chest x-ray
- Need for mechanical ventilation or other support
- Need for pressure support

Day 1 Assessments

- Vital Signs q 6 hours (0000,0600,1200, 1800)
- FiO2
- PaO2 if available

- Chest x-ray – if available
- Heart rate and any arrhythmias noted via telemetry
- Evidence of successful/ongoing block
- Horner's syndrome
- Current rate of infusion
- Concomitant Medications
- Vasopressor use
- Adverse Events
- Labs: CRP, IL-1 beta, TNF-alpha, IL-6, ABG (if on vent)
- Production of nitric oxide via Niox

Day 2 Assessments
- Vital Signs q 6 hours (0000,0600,1200, 1800)
- FiO2
- PaO2 if available
- Chest x-ray- if available
- Heart rate and any arrhythmias noted via telemetry
- Blood gas if available
- CRP
- Evidence of successful/ongoing block
- Horner's syndrome
- Current rate of infusion
- Concomitant Medications
- Vasopressor use
- Adverse Events
- Production of nitric oxide via Niox

Day 3 Assessments
- Vital Signs q 6 hours (0000,0600,1200, 1800)
- FiO2
- PaO2 if available
- Chest x-ray – if available
- Heart rate and any arrhythmias noted via telemetry
- Evidence of successful/ongoing block
- Horner's syndrome
- Current rate of infusion
- Concomitant Medications
- Vasopressor use
- Adverse Events
- Labs: Labs: IL-1beta, TNF-alpha, IL-6, ABG (if on vent), CRP
- Production of nitric oxide via Niox

Day 4 Assessments
- Vital Signs q 6 hours (0000,0600,1200, 1800)
- FiO2
- PaO2 if available
- Chest x-ray- if available
- Heart rate and any arrhythmias noted via telemetry
- Blood gas if available
- CRP

- Evidence of successful/ongoing block
- Horner's syndrome
- Current rate of infusion
- Concomitant Medications
- Vasopressor use
- Production of nitric oxide via Niox
- Adverse Events

Day 5 Assessments
- Vital Signs q 6 hours (0000,0600,1200, 1800)
- FiO2
- PaO2 if available
- Chest x-ray-if available
- Heart rate and any arrhythmias noted via telemetry
- Evidence of successful/ongoing block
- Horner's syndrome
- Current rate of infusion
- Concomitant Medications
- Vasopressor use
- Adverse Events
- Labs: Labs: IL-1beta, TNF-alpha, IL-6, ABG (if on vent), CRP
- Production of nitric oxide via Niox

Follow-up assessment Day 90
- Survival status
- SF 36
- Adverse events
- Ongoing issues/oxygen use/rehab

Section 8.0 Drug Dosage:

There will be no dosing adjustments to the continuous perineural catheter or initial bolus injection. The bosting of the block has been reduced to the minimum effective dose.

SGB Drug doses:
Initial perineural bolus injection will include clonidine 100 mcg, decadron PF 5mg, and 0.25% bupivacaine 5 ml.

Perineural catheter:
Infusion of 0.2% bupivacaine will be initiated at 2ml/hr for 5 days.

All medications are FDA approved. Standard orders for perineural blocks will be entered into the EMR system. Pharmacy responsible for ICU/progressive care will dispense orders for the medication used in the SGB. Pharmacist in ICU/progressive care will fill Cadd pump infusion catheter once per day per standard procedure in the ICU/progressive care.

Section 9.0 Adverse Event Reporting Guidelines:

The initial procedure will be stopped and the patient will be withdrawn if any of the following occurs; vasopressor or unresponsive hypotension, intrathecal injection, pneumothorax, expanding hematoma, allergic reaction, or cardiac arrhythmias. For continuous infusions, the catheter will be removed and the patient will be withdrawn if any of the following occur: local systemic toxicity, seizure, catheter migration to intravascular or intrathecal space, expanding hematoma, vasopressor unresponsive hypotension, symptomatic bradycardia, insertion site infection. Any adverse events will be treated with Nebraska Medicine standard of care procedures. Subjects can also voluntarily withdraw at any time. The PI can also withdraw any subject that is not felt to be a suitable candidate for the study.

Serious adverse events directly related to block will result in withdrawal. Directly block related serious adverse events include: local systemic toxicity, seizure, serious allergic reaction, expanding hematoma, or catheter migration to intravascular or intrathecal space, insertion site infection. As well, patients will be withdrawn if the patient develops medication unresponsive bradycardia or hypotension. This may not be directly related to block but discontinuation of infusion may facilitate resuscitation of patient. Expected complications may include voice hoarseness, ipsilateral eyelid drooping, mild pain at site of catheter, and blurred vision. Occurrence of expected complications will not result in withdrawal from study unless demanded by the patient.

Section 10.0 Statistical Considerations:

Statistical considerations for primary objective, the analysis would include means/medians (standard errors, IQRs) at each time point - and also represented by error bars - and comparisons using t test or the Mann-Whitney U test as appropriate. Multivariate analyses using Generalized estimating equations (GEE) and to compare longitudinal changes in the two groups adjusting for confounders and as well as ANCOVA based regression to measure before and after changes. Kaplan-Meier survival methods to measure time to defined thresholds and Cox regression to assess any impact of confounders.

For safety - AE's will be assessed by providing descriptive statistics related to their frequency (summarized by occurrence, percentage of occurrence, severity, seriousness, outcome, relation to treatment, start time summary, duration of AE analysis) as well as graphically via box plots and cumulative incidence plots indicative of distributions in the two trial groups. Non-parametric methods (e.g. Fisher Exact testing) will be used to statistically compare the period frequency of events between the two groups. In general, timely analysis, by creating summaries of adverse events and other safety measurements such as relevant vital signs, ECG, Laboratory abnormal findings will be done to keep a check on the increase in intensity of observations taken at baseline and/or new findings arisen after baseline.

Secondary measures:
Occurrence of cardiac arrhythmias, need for mechanical ventilation and/or ECMO as well as overall survival will be compared using time-to-event based methods (e.g. Kaplan-meier curves). The expectation is that any non-statistically significant but implied trends will be evaluated in larger phase IIb /III trial that will follow.

Stopping Rules:
We have computed stopping rules for safety, from a statistical standpoint, standpoint based on the known background rate to help support export opinion. The stopping rules for this study are based on the prospectively accumulated safety data collected from each individual patient and utilize the hypothesis testing approach. The idea is to rule out an observed event rate that is higher than the background event rate and to stop the trial if an excessive event rate is observed. For our plan to enroll 16 subjects, we assume (based on literature) that the background rate for the known risk of our experimental intervention is 10%. Based on this we have constructed a stopping rule plan (See Table below) based on the background rate of the main Serious Adverse Drug Reaction or Event SAE/ADR of 10%.

Our DSMB is empowered to stop the trial whenever they deem fit to protect the safety of patients. However, based on our plan, the DSMB will consider adopting a stopping rule that evaluates the rate of SAE/ADR after 5 enrollments,

and thereafter with each enrollment and SAE/ADR reported will require stopping/*suspension* of trial entry if the observed rate of SAE/ADR is sufficient to reject the null hypothesis that the true SAE/ADR proportion (P) is 10% or less in favor of the (one-sided) alternative hypothesis that the true SAE/ADR proportion is more than 10%. The table below depicts the stopping guidelines. Exact binomial methods are used to compute the p values and confidence limits. One-sided lower 90% confidence limit is calculated.

Number of Subjects Enrolled in the Study	Number of SAE/ADR Needed to Reject Null Hypothesis	Observed Rate of SAE/ADR (%)	One-sided p values	Lower 90% Confidence Limit
~5	2	40%	0.0815	11.22%
6-10	3	30%	0.0702	11.58%
11-15	4	27%	0.0556	12.18%
16-20	5	25%	0.0432	12.69%

Thus, for instance, if 2+ SAE/ADR events are observed in less than and equal to 5 subjects enrolled, the lower confidence limit of 11.22% will exceed the 10% background rate. The stopping rule for safety will be triggered and the study should be suspended/stopped at the discretion of the DSMB.

Section 11.0 Records to be kept: A list of all records, including flow sheets, data collection forms/instruments, summary and evaluation forms will be locked in the study coordinator's office. The subject list will be maintained by the study coordinator. The data from the electronic medical record will be retrieved and entered into the REDCAP database by research personnel.

Section 12.0 Patient Consent: The consent form must adhere to the guidelines established by the Institutional Review Board of the University of Nebraska Medical Center. The most current version of ICF will be located in the IRB application #523-20-FB. Electronic versions of ICF will be used in the event a LAR is needed to sign consent.

Subjects and/or LAR will be approached while subject is in the ICU/progressive care. If subject is unable to participate in the consenting process, the LAR will be contact via telephone and/or video chat. Consents will be sent to LAR electronically. PI and/or Sub-I will be present for all consenting process regardless is the ICF process takes place in person or video digital presence.

The subject will be in the ICU/progressive care room. A one-on-one conversation will be had between the subject & PI/Sub-I, of approximately 30 minutes to review the ICF. Then the subject will be given time alone to read over consent and ask any additional questions. If the LAR is not present in the ICU/progressive care, the LAR will be spoken to over the telephone. An electronic ICF will be sent to the LAR prior to the phone conversation. The phone conversation will last approximately 30 minutes to review the ICF. The LAR will be instructed to hang up and read the ICF in its entirety. A return call will be placed to the LAR at a designated time. Additional questions will be answered before electronic signature is done by LAR.

Section 13.0 Study and Safety monitoring DSMB

A DSMB has been constituted that includes: Dr. Robert Lobato, Dr. Madhuri Are, and Danstan Bagenda, Ph.D., whose responsibility will be to review continually the safety and efficacy data, as well as the other aspects of the trials

conduct. The DSMB has been charged with making recommendations regarding early suspension or termination of age trial if there is unexpected evidence of safety concerns or dramatic intervention effect. With this particular phase, in addition to proper conduct of the trial as indicated in the protocol the DSMB will primarily be concerned with monitoring adverse effects and assessing any potential adverse events with respect to patients safety at all times and advising study continuation. The study PI will, nevertheless, still shoulder the responsibility of immediately reporting potential severe adverse effects to the DSMB and ultimately all SAEs to the IRB. Weekly or immediately - at the urgent earliest opportunity-upon each potential SAE whichever occurs first, the DSMB will review the accumulating numbers and types of severe adverse-including assessing there relatedness to study intervention and recommend any analyses by the study biostatistician-pooled , by treatment group, or disaggregated as may be requested, for review against the specified stopping rules and to advise any concerns and course of action with regard to any individual of collective patient safety. The DSMB will be supported by Danstan Bagenda, a trained Biostatistician with long experience working with NIH study DSMBs for phase I, II and III clinical trials, and who, although a Co-I with the study, has no clinical responsibility for care with any patients at UNMC.

Section 13.0 References

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Appendix A.

Protocol for stellate ganglion (SG) blockade in coronavirus disease (covid-19) patients

Purpose:

To prevent morbidity and mortality related to moderate to severe covid-19 infection.

Responsibilities:

The attending intensivists will determine if a covid-19 patient is displaying indications for stellate ganglion block.

APS will be consulted to urgently place the stellate ganglion block.

A left sided SGB continuous perineural catheter will be placed by either ultrasound guided or fluoroscopy guided technique at the discretion of the APS attending in consultation with the chronic pain attending.

Procedure:

The attending proceduralist and resident assistant will perform the SGB at bedside under the following conditions:

1. The block will only be performed in the intensive care setting.
2. Intensive care nurse will provide patient monitoring and assistance during the procedure.
3. The proceduralist will exam and record pupillary size prior to procedure and 20 minutes post injection.
4. For fluoroscopy guidance, the radiology technician will provide imaging assistance during the procedure.
5. A Logiq R7 machine will be brought to the patient's bedside by the APS attending for ultrasound guidance.
6. All equipment will be decontaminated with bactericidal/virocidal wipes prior to exiting the patient's room and immediately upon exiting the room.
7. Personnel involved in the procedure will don and doff N-95 respirators, gowns, gloves, and faces shields and strictly adhere to Nebraska Medicine covid-19 isolation/precautions for this non-aerosol generating bedside procedure.
8. Standard ASA monitors and ACLS resuscitative equipment will be immediately available.
9. A norepinephrine solution will be ordered by proceduralist and at bedside in order to treat potential hypotension associated with SGB especially in a baseline unstable patient.
10. Pain provider will also bring standard prn IV bolus vasopressors including phenylephrine and epinephrine.

The SGB perineural catheter will be placed using standard sterile technique.

1. Initial perineural bolus injection will include clonidine 100 mcg, decadron PF 5mg, and 0.25% bupivacaine 5 ml.
2. A Cadd perineural infusion 0.2% bupivacaine will be initiated at 2ml/hr for 5 days.
3. The proceduralist will stay at the patient's bedside for 20 minutes to monitor for signs of cardiovascular instability of respiratory distress. Following this period, the patient may be returned to standard ICU/PROGRESSIVE CARE reassessment regimens.
4. The patient will be monitored for neck hematoma formation by the nurse with neck soft tissue reassessment every 15 min for 1 hour.
5. APS providers will round on the patient daily and provide standard perineural catheter maintenance as well as record of pupillary size.
6. APS will discontinue and remove the catheter after 5 days have elapsed.

Appendix. B

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:**_____

ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?

○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○
○ Somewhat worse now than one year ago
Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks

Yes, Limited a Lot | Yes, Limited a Little | No, Not Limited at all

Walking one block

Yes, Limited a Lot | Yes, Limited a Little | No, Not Limited at all

Bathing or dressing yourself

Yes, Limited a Lot | Yes, Limited a Little | No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

Yes | No

Accomplished less than you would like

Yes | No

Were limited in the kind of work or other activities

Yes | No

Had difficulty performing the work or other activities (for example, it took extra effort)

Yes | No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

Yes | No

Accomplished less than you would like

Yes | No

Didn't do work or other activities as carefully as usual

Yes | No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all | Slightly | Moderately | Severe | Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

None | Very Mild | Mild | Moderate | Severe | Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all | A little bit | Moderately | Quite a bit | Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time

None of the Time

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
-

None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I am as healthy as anybody I know
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

I expect my health to get worse
Definitely true | Mostly true | Don't know | Mostly false | Definitely false

My health is excellent
Definitely true | Mostly true | Don't know | Mostly false | Definitely false