TITLE: Effect of Oral Minocycline in Patients with Acute Stroke: A Randomized Open-label, Prospective Trial

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INTRODUCTION:

Numerous animal studies and human clinical trials have suggested that Minocycline may possess neuroprotective properties against various nervous system injuries, including stroke, trauma, demyelination, degeneration, and infections. At Maimonides Medical Center, Minocycline was utilized as a standard treatment for patients with acute stroke from 2007 to 2019. However, due to the need for more definitive literature and guideline support, such as convincing large-scale randomized clinical trial data for efficacy, its use was discontinued in April 2019 after a program-wide review and assessment. Notably, no significant adverse effects were reported or observed during the abovementioned period.

To determine the potential clinical benefits of routine oral Minocycline use of 200mg daily for five days after stroke symptom onset, a retrospective chart review and statistical analysis of the cohorts before and after the discontinuation of Minocycline in April 2019 was conducted. Specifically, our study aimed to measure acute stroke patients' in-hospital mortality and hemorrhagic transformation rates.

The Maimonides Jaffe Comprehensive Stroke Center Quality Improvement (QI) analysis revealed an overall increase in in-hospital mortality rates from 2018 to 2022, which the ongoing COVID pandemic and other factors may further complicate. Thus, our study will delve into a retrospective chart review to compare clinical outcomes measured by in-hospital mortality and discharge NIHSS.

BACKGROUND AND SIGNIFICANCE:

Stroke is the fifth leading cause of death and the leading cause of severe long-term disability in the US. The stroke-related cost is estimated to be $53 billion between 2017 and 2018 and keeps increasing every year1. Intravenous Alteplase (tPA) is the only FDA-approved treatment for acute ischemic stroke. However, Tenecteplase (TNK) has been endorsed and widely accepted as the alternative, if not superior, choice of thrombolytic therapy. In addition, many neuroprotective trials have been conducted, including those for stroke patients. However, effective treatments or agents offering significant neuroprotective benefits are still elusive.

Minocycline is an FDA-approved second-generation, semi-synthetic broad-spectrum antibiotic that exhibits neuroprotective effects with multiple proposed mechanisms of action in various injury models2. Clinically, Lampl et al. observed that a 5-day course of oral minocycline significantly reduced neurological impairment in acute ischemic stroke3. Hemorrhagic transformation rates did not differ by treatment group. Acute hemorrhagic stroke accounts for about 12 – 20 % of all types of strokes, accounting for about 2 million cases worldwide annually, leading to high mortality and disability rates of up to 50%. Early initiation of oral Minocycline continues to be promising in Intracerebral hemorrhage (ICH)4.

At our institution, since the Lampl study, we have used Minocycline for all eligible patients with ischemic strokes. Our experience has been that patients treated with IV alteplase or catheter-based therapies given oral Minocycline (200 mg once daily for five days) may have lower rates of hemorrhagic conversion of ischemic stroke.

However, this is not a widely accepted stroke care standard, given its limited clinical evidence from large-scale randomized placebo-controlled trials (RCTs). Therefore, after a consensus discussion among stroke clinicians at our institution, we discontinued the program-wide use of Minocycline in March 2019. Subsequently, we observed higher rates of hemorrhagic conversion and increased mortality amongst our stroke patients since then, coinciding and initially attributed to the Covid-19 pandemic and our patient severity and comorbidity increase. In this study, we set out to conduct a prospective analysis of acute stroke patients' clinical outcomes measured by NIHSS and mRS on admission and at discharge and 90 days and the rate of hemorrhagic transformation of ischemic strokes with/without IV thrombolytic and thrombectomy in addition to all-cause mortality at 30 days. The study will prospectively enroll all eligible stroke patients consecutively assigned to either Minocycline treatment along with the standard treatment group or the standard treatment group alone (from Sept 2023 to June 2025), comparing the above clinical outcomes. We will have interim analysis at 6-month intervals for safety and primary outcomes threshold examination. The results of this study may help us better understand the efficacy and safety profile of Minocycline in acute stroke treatment in both ischemic and hemorrhagic strokes, which may improve the clinical stroke care at our institution and beyond.

STUDY OBJECTIVES:

Primary:

- NIHSS score and mRS scores on admission and at discharge (including mortality, mRS=6) and on day 90 post-stroke

Secondary:

- To determine if Minocycline decreases rates of all (symptomatic and asymptomatic) intracranial hemorrhage in patients treated with intravenous alteplase or catheter-based therapies compared to patients receiving standard care for stroke.
- To compare the in-hospital and 30-day mortality rates in patients admitted for acute stroke between those receiving Minocycline and those receiving standard care.

HYPOTHESIS:

When combined with the standard care treatment, Minocycline's neuroprotective effects improve the clinical outcomes, including the mortality, of acute stroke patients compared to the standard stroke care without Minocycline.

STUDY DESIGN:

Subjects: Patients with clinical suspicion of stroke presenting in patient – both ischemic and hemorrhagic or computer tomography consistent with acute stroke consistent with WHO guidelines.

Serious Adverse Events:
Some rare and serious side effects of the 5 days course of Minocycline include diarrhea, skin reaction, blurring visions and anaphylaxis allergic reaction, and kidney disease.

For serious adverse events, we will file as soon as possible (within 24 hours) to PI and no later than 15 days after initial receipt of the SAE. All SAEs will be reported to the IRB within 5 business days as reportable event.

Interim Reporting:
Data from the trial will be reviewed periodically and continuously. Any adverse events will be reported to the IRB, and the trial may be potentially terminated if deemed clinically appropriate. Pre-planned interim analyses will be carried out at 6, 12, 18 and 24 months for safety and efficacy outcomes. The independent DSMB members will carry out the periodic assessments mentioned above.

Eligibility Criteria:

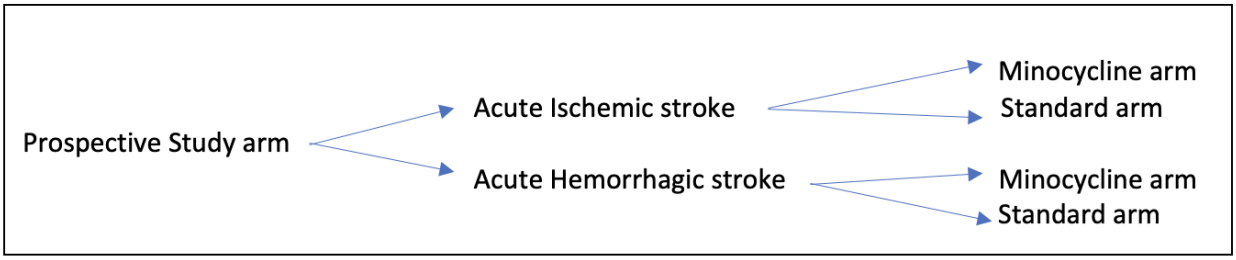
- **Inclusion criteria:**

1. Age >/=18
2. Acute onset neurological deficit consistent with acute ischemic stroke or on imaging consistent with acute ischemia as defined by WHO guidelines
3. Acute onset of neurological deficits with intracerebral Hemorrhage on imaging consistent with intracerebral bleed
4. The onset of symptoms less than 24 hours
5. Measurable neurological deficit using NIHSS

- **Exclusion criteria:**

1. Clinically not suspect stroke.
2. Allergic to the Tetracycline group of medications or Intolerance to Minocycline
3. Pregnancy or suspected pregnancy
4. Previous history of intolerance to minocycline
5. Acute or chronic renal failure
6. Any patients with contraindications to undergo CT/ MRI
7. Life expectancy less than one year or severe co-morbidities or comfort measure only (CMO) on admission
8. Pre-existing infectious disease requiring antibiotics
9. Inability to tolerate enteral medications/feeds
10. Patient/ family refusal

Design:



The prospective study will enroll 1120 patients who arrive in the ER at Maimonides Hospital for suspected acute stroke. After obtaining informed consent, 1120 patients will be enrolled from August 2023 to July 2025. Consecutive randomization will be done, and 560 patients will be assigned to each arm, the Minocycline and Standard arms. The 560 patients in the Minocycline arm will receive Minocycline 200 mg every 24 hours for five days in addition to standard care, while the Standard arm will accept only standard care. NIHSS and mRS scores will be measured on presentation (baseline) and at discharge. A comparison will be made between both arms in both studies for their significance. Statistical analysis will be done with the help of a Maimonides statistician. Interim research will be conducted every six months for outcome significance and safety measures (30-day mortality and symptomatic hemorrhagic conversion).

Randomization: Consecutive randomization will be done.

Blinding Technique: Evaluator-blinded study

Data Collection Procedures:
Patients getting admitted at the Medical Center for acute stroke will be evaluated, and their eligibility for the trial will be assessed. Then the eligible patients will be randomly assigned to the Minocycline or the Standard group in their respective arms consecutively. Acute Ischemic and Hemorrhagic patients will be treated with Minocycline along with standard care versus standard care alone. Patient demographic details and information on co-morbidities are collected. Their NIHSS and mRS scores will be measured at the time of presentation and discharge and again at 30- and 90-days post-discharge. All-cause mortality will also be obtained at 30 days and 90 days. The outcomes are documented, and the results will be analyzed.

Data Analysis:
Data analysis will be performed with the assistance of the MMC biostatistician.

All numeric variables will be summarized with mean and 95% confidence interval where appropriate and median and IQR if necessary. All categorical variables will be outlined with frequency and percentage. Continuous risk factors or demographic variables will be compared across groups using a t-test or Wilcoxon rank sum test. Categorical risk factors and demographics will be compared between groups using a chi-square or Fisher exact test.

The primary outcome of reduced NIHSS and mRS as discharge will be evaluated using a student's T-test. The outcome of mortality will be evaluated using a Fisher exact test. 90-day outcomes will be evaluated similarly. To control for additional risk factors, including baseline NIHSS and mRS, we will also create a generalized linear model with a normal link function for continuous outcomes, controlling for risk factors significantly different between groups. For mortality, we will use a generalized linear model with a logistic link function to control for risk factors that vary considerably between groups.

Sample Size:
Target power: 0.8
Actual power: 0.800
Alpha: 0.05
Assumed population means 3.2 for the placebo group and 2.9 for the Minocycline group (with an expected difference between the population's means is 0.51)
Calculated size: 560 in each arm with a total of 1120 patients after considering a 10% attrition rate.

Expected Outcomes:
When combined with the standard care treatment, Minocycline's neuroprotective effects improve the clinical outcomes, including the mortality, of acute stroke patients compared to routine stroke care without Minocycline.

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