Quantitative Assessment of Painful Diabetic Peripheral Neuropathy after High Frequency Spinal Cord Stimulation: (QUANT) HF10 Study

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General Study Information

Principal Investigator: Narayan R. Kissoon, MD
Co-Investigators: [redacted]

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Research Question and Aims

Hypothesis: Painful lower extremity diabetic peripheral neuropathy (DPN) patients treated with high frequency spinal cord stimulation (HF10 SCS) will have improvements in lower extremity peripheral nerve function.

Aims, purpose, or objectives:

1. To determine if patients with DPN have improvements on sensory examination by assessing both small and large fiber modalities after being treated with HF10.
2. To determine if patients with DPN have improvements in small fiber nerve function after being treated with HF10 SCS as measured by the quantitative axon reflex sweat test (Q-SWEAT).
3. To determine if large fiber nerve function improves after being treated with HF10 SCS as measured by Nerve Conduction Studies of the lower extremities.
4. To determine if lower extremity perfusion improves after being treated with HF 10 SCS as measured by Laser Doppler flowmetry.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Spinal cord stimulation (SCS) has been shown to be effective and is an FDA approved treatment for neuropathic pain of the extremities.[1, 2] Randomized trials have demonstrated efficacy in providing pain relief using SCS in patients with neuropathic pain related to diabetic peripheral neuropathy and is an FDA approved treatment for intractable pain related to diabetic peripheral neuropathy.[3-5] Length dependent distal symmetric peripheral polyneuropathy is the most common form of diabetic neuropathy and the pathogenesis is related to vascular (endothelial dysfunction with microvascular ischemia) and metabolic factors (hyperglycemia resulting in oxidative stress).[6-12] These factors lead to progressive neuronal degeneration with the distribution and morphology of fiber loss suggesting ischemia, which is not similar to other diffuse metabolic diseases.[13-19] Vascular physiologic changes such as a reduction of endoneurial oxygen tension has been observed in patients with advanced diabetic polyneuropathy and differences were found between painful and painless diabetic peripheral neuropathy.[20, 21] Animal models of DPN have demonstrated spinally mediated hyperalgesia and allodynia.[22] Pain relief with SCS has been shown to correlate with levels of various neurotrophic factors in the cerebrospinal fluid (CSF).[23, 24]

Growing evidence supports the use of SCS in the treatment of pain-related ischemia with approval in Europe for treatment of refractory angina pectoris and critical limb ischemia.[25] A study by Jivegard et al demonstrated significant pain relief at 18 months for patients with nonsurgical critical limb ischemia when treated with SCS and showed lower amputation rates when excluding patients with arterial hypertension.[26] A study by Broseta et al had shown better outcomes with SCS for critical limb ischemia in patients without hypertension when compared to patients with hypertension.[26, 27] In addition, patients with critical limb ischemia treated with SCS had poorer outcomes with a baseline foot transcutaneous oxygen (TcPO2) < 10 mmHg and clinical improvement coincided with an increase in TcPO2.[28, 29] Other randomized trials not taking into account TcPO2 and history of hypertension did not show any difference between SCS with medical management and medical management alone.[30, 31] A meta-analysis pooled from these prior randomized controlled trials (RCTs) demonstrated significant limb salvage benefit suggesting the individual RCTs were underpowered.[25, 31] Several studies suggest a correlation of pain relief with increased blood perfusion.[32, 33]

In animal models with vasospasm, SCS has been shown to reduce peripheral ischemia.[34, 35] The potential improvement in extremity perfusion is believed to result from two mechanisms.[36-39] First, SCS attenuates sympathetic outflow resulting in decreased vascular resistance and increased peripheral blood flow.[36, 38, 40] Alternatively, SCS can lead to alterations in the ERK and AKT signaling pathways along with GABA release in the grey matter of the spinal cord that results in antidromic activation of primary afferent fibers leading to peripheral vasodilation.[38, 41-43] These changes in primary afferent activity are mediated by CGRP release and TRPV1 containing sensory neurons, which can result in nitric oxide-induced endothelium dependent vasodilation.[44-47] In animal models of diabetes, SCS has been shown to increase peripheral blood flow.[48] However, the vasodilatory response was attenuated and thought to be related to the extent of peripheral nerve and autonomic dysfunction.[39, 48] The vasodilatory response from SCS appears to be dose dependent with high frequency SCS demonstrating greater increases in cutaneous blood flow when compared to lower frequencies.[36]

In patients with diabetes and critical limb ischemia +/- diabetic neuropathy, improvements in pain relief correlated with increases in peripheral blood flow.[49-51] In patients with diabetes and critical limb ischemia, the severity of autonomic neuropathy was inversely related to the success of SCS therapy (both limb salvage and pain relief), independent of the stage of the peripheral artery disease.[52] In a small case series by de Vos et al 2009, a group of patients with DPN observed significant pain relief, but only a non-significant trend of increased perfusion was seen at 6 months when compared to baseline.[53]

In animal models, SCS has been shown to demonstrate improvements in neurological examination as demonstrated by mechanical withdrawal thresholds (marker of allodynia) and compression withdrawal thresholds (marker of hyperalgesia).[37, 54] These improvements were frequency dependent with changes during treatment using low frequency SCS likely a result of supraspinal mechanisms and changes during higher frequency SCS likely as a result of spinal mechanisms.[54, 55] In a diabetic animal model, high frequency SCS resulted in a delayed effect on pain related behavioral outcome in chronic DPN (mechanical withdrawal thresholds).[37]

HF10 SCS is an FDA approved treatment that has been shown to be superior to traditional lower frequency SCS in the management of chronic back pain and neuropathic lower extremity pain.[56] Preliminary data has

suggested that treatment of chronic intractable pain related to peripheral polyneuropathy with HF10 SCS also resulted in improvements on neurological examination (predominantly sensory modalities).[57]

Our hypothesis is that patients with painful DPN will have improvements in sensory examination and the improvements will predominantly be in small fiber nerve function. In addition, these improvements may be objectively assessed with small fiber sudomotor testing (Q-SWEAT) as patients with length dependent diabetic peripheral neuropathy have been shown to have sudomotor dysfunction along with progressive sweat gland dennervation.[58, 59] The changes in Q-SWEAT will be an objective marker of small fiber nerve function and the proposed mechanism is through increases in perfusion of the peripheral nerves secondary to vasodilation induced by high frequency spinal cord stimulation. As the HF10 SCS leads are placed at the level of the thoracic segments, it is unlikely to result in any improvements in hand symptoms. Also, SCS would be unlikely to improve upper extremity symptoms in DPN because upper extremity symptoms in DPN are usually related to superimposed mononeuropathies (median neuropathy at the wrist or ulnar neuropathy at the elbow).[60]

Patients with DPN frequently have large nerve fiber involvement as well as the small nerve fiber involvement that will be assessed with Q-SWEAT. Large nerve fiber function can be assessed with nerve conduction studies.

The proposed improvements in peripheral nerve function may occur in both an immediate (days to months) and delayed (months to years) response. Some of the more proximal nerve fibers may be in an area of penumbra where chronic neuropraxia (dysfunctional but still intact) is causing the impairments. With improved perfusion of these fibers, recovery of function may happen more quickly (days to months). In the more distal nerves fibers, the deficits are more likely related to chronic axonotmesis (axonal damage with nerves intact) or neuronotmesis (both axonal and nerve damage), which would likely take more reperfusion time to demonstrate improvements (months to years) with deficits related to axonotmesis. The pain improvement effects of HF10 SCS are sustained with long term data of success with HF10 SCS being demonstrated up to 24 months.[61]

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

Patients with intractable neuropathic lower extremity pain related to DPN that fulfill inclusion and exclusion criteria (see below) will be considered for participation in this prospective feasibility study. Baseline testing will be performed to exclude confounding factors that may affect outcomes (figure). All patients that are candidates for SCS undergo a spinal cord stimulation trial as part of standard clinical care with all of the FDA approved indications. If the patient is deemed a candidate and complying with this standard clinical practice, the patient will undergo a HF10 SCS (Nevro Senza®) trial lasting up to 14 days with an external stimulator to determine short term response.[56] Patients with 40% or greater pain reduction from baseline will be eligible to proceed to permanent implantation.[56] Patients with HF10 SCS will receive 30 μs pulses delivered at 10,000 Hz with amplitude adjusted to optimal analgesic response. Programming will occur postoperatively and as needed based on patient feedback in standard clinic visits.[56] At 6 month follow-up, paresthesia mapping will be performed during the programming visit in which the subthreshold SCS will be temporary increased during a 10 minute protocol to a perceived level to determine the dermatomal stimulation pattern with the SCS lead placement.

Implant Procedures
The SCS implant will follow standard clinical practice for these FDA approved indications. Two percutaneous leads will be placed in the posterior spinal epidural space under radiographic guidance and attached to either an external stimulator (trial phase) or a subcutaneously implanted impulse generator (IPG). The distal tip of one lead will be placed at the top of the T8 vertebral body and the second lead tip will be placed at the mid T9 vertebral level for maximal electrode coverage at the T9/T10 junction.[56] A subcutaneous pocket will be created using standard surgical techniques for placement of an IPG. The leads, anchored to the supraspinous fascia, will be tunneled to the pocket site and connected to the IPG. Intraoperative impedance testing will be performed to ensure electrical integrity.[56]

Outcome Assessments
Adverse events will be monitored throughout the study (e.g. infection, lead migration). Lead migration will be defined as loss of efficacy that could not be remedied by reprogramming and confirmed radiologically.[56] Baseline testing will be performed either prior to SCS trial or a minimum of two weeks following removal of SCS trial leads and prior to SCS implant. During outcome assessments, the spinal cord stimulator will remain active and any medications that can impact autonomic testing will be discontinued prior to each test. Assessments of pain will be made with the numeric rating scale (NRS) for each of the time points. The patient will be contacted at 5 and 11 months to set up in-person assessment appointments. At this time, the NRS will be used. If the NRS is $\geq$3 the principal investigator will be notified and the patient will have an appointment for a SCS assessment prior to the 6 and 12 month assessment. Neuropathic symptoms will be monitored with the Neuropathy Symptoms and Change (NSC) scale at 6 months and 12 months to assess impact on neuropathic pain (figure).[62] Patient Health Questionnaire (PHQ9) will be assessed at baseline, 6 months and 12 months to monitor for the presence and severity of depression. A body mass index (BMI) and Hemoglobin A1C (HgA1C) will be done at baseline and at 12 months. The presence of allodynia and/or hyperalgesia will be monitored throughout the course of the study with the modified Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS).[63] Small fiber sudomotor function with Q-SWEAT will be assessed periodically during the study (baseline, 6 months, and 12 months) (figure).[28, 53, 58, 59, 64, 65]

Gross neurologic function will be assessed by a board certified neurologist at baseline, 6 months, and 12 months, and the neuropathy impairment score (NIS) of the lower limbs with lower limb function test (LLF) will be calculated for an objective comparative assessment.[66, 67] EMG will be performed at baseline (partly to exclude mimickers of DPN) and at 12 months to compare nerve conduction studies (NCS) for an objective assessment of large fiber nerve function(figure).[67] Only the NCS of the lower limb will be performed with the EMG at 12 months (no needle EMG will be performed at 12 months). The Oswestry Disability Index (ODI) will be used as a gross functional assessment at each of the time points.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

1. Clinical research coordinator to aid in implementation of the study
2. Periodic testing (Q-SWEAT and Laser Doppler flowmetry) will be performed in the Clinical Research Unit (CRU)

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 20 patients over the course of a 2 year enrollment period (3 years in total for completion of study).

Subject population (children, adults, groups): Patients with the FDA approved indication of medically intractable painful DPN age 18 and over that are appropriate surgical candidates and without severe autonomic neuropathy or psychiatric comorbidity that would preclude SCS implant.

Inclusion Criteria:

- ≥ 18 years of age
- Type 2 diabetes mellitus
- Refractory predominantly lower extremity neuropathic pain for > 1 year
- Presence of length dependent peripheral neuropathy on sudomotor testing (Q-SWEAT)
- Completed spinal cord stimulation trial with 40% or greater pain reduction from baseline
- Failed medication trials or contraindication to gabapentinoid medications (gabapentin, pregabalin) and/or serotonin/norepinephrine reuptake inhibitors (tricyclic antidepressant (TCA) or duloxetine or venlafaxine)
- Average pain score on a numeric rating scale of ≥ 5 (with 0 representing no pain and 10 the worst pain imaginable)
- Appropriate surgical candidate for SCS[56]

Exclusion Criteria:

- Severe Autonomic Neuropathy as measured by the composite autonomic scoring scale (10 point scale) with a score ≥ 7[52, 64]
- History of sympathectomy[52]
- Uncontrolled arterial hypertension (Systolic Blood Pressure >160)[26, 27]
- Baseline Foot TcPO2 < 10 mmHg to exclude patients with severe peripheral arterial disease[28, 29]
- Hemoglobin A1c > 8%[68, 69]
- Stable opioid regimen with oral morphine equivalent ≥ 100 mg/day[70]
- Alternative principle cause for peripheral neuropathy or lower extremity neuropathic pain
- Disruptive psychiatric disorder (screened for during preoperative psychiatric evaluation)[56]
- Pending litigations[56]

- Women of child bearing potential unwilling to use contraception or found to be pregnant as part of perioperative screening
- Patients unable to hold medications that would impact autonomic testing

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☒ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
Volume per blood draw: _____ml
Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: 01/01/2015 to 6/30/2022

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☒ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.

Examples
- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number	X	
Medical device identifiers and serial numbers	X	
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes		

Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☒ No statistical information. *If checked, please explain*: feasibility study.

Power Statement:

This is a feasibility study and so a power analysis was not performed.

Data Analysis Plan: Demographic data will be reported with descriptive statistics, including means with SD's for continuous data and percentages and counts for categorical data. Assuming a normal distribution, two-sided paired *t* tests and analysis of covariance (ANCOVA) will be used to compare means in VAS/NRS pain scores, NSC, ODI, NIS, LLF, and S-LANSS scores at the corresponding time points as the primary endpoints(figure). In addition, two-sided paired *t* tests and analysis of covariance (ANCOVA) will be used to compare means for amplitudes (mA) and conduction velocity (m/s) on NCS with EMG at baseline and 12 months post-implant. The secondary endpoints will be assessed with two-sided paired *t* tests and analysis of covariance (ANCOVA) for latency (min) and sweat output (µL/cm²) on Q-SWEAT and arbitrary perfusion units on Laser Doppler flowmetry (p.u.) at baseline, 6 months, and 12 months post-implant.

Endpoints:
Primary: Changes in VAS/NRS, NSC, ODI, NIS, LLF, and S-LANSS.
Secondary: Changes in latency (min) and sweat output (µL/cm²) on Q-SWEAT, arbitrary perfusion units (p.u.) on Laser Doppler flowmetry, and amplitudes (mA) and conduction velocity (m/s) on NCS when compared to baseline. Changes in BMI, HgA1C and PHQ9 scores when compared to baseline.
FIGURE

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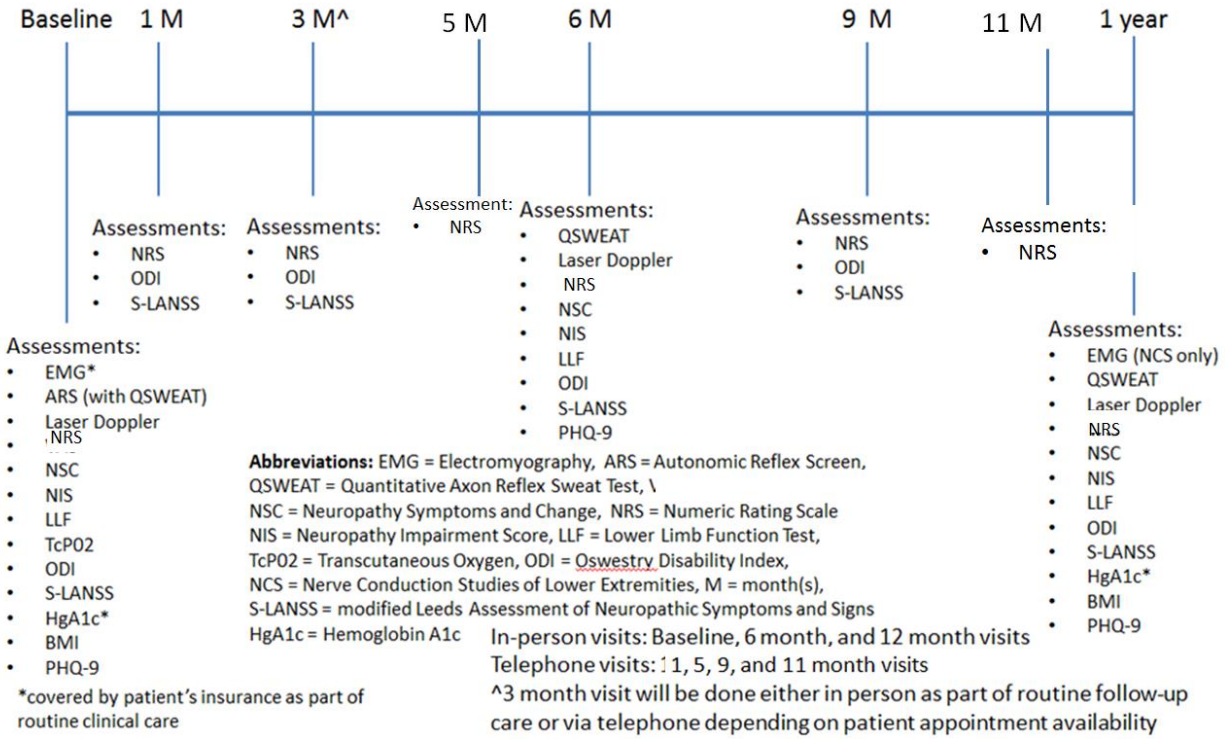
Quantitative Assessment of Painful Diabetic Peripheral Neuropathy after High Frequency Spinal Cord Stimulation: (QUANT) HF10 Study



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