INJECTION THERAPY IN CARPAL TUNNEL SYNDROME PATIENTS: LOOKING FOR EFFECTIVENESS THROUGH QST AND F-MRI CHANGES

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Carpal tunnel syndrome (CTS) is the commonest compression neuropathy.

Local injection therapy improves clinical symptoms.

The possible mechanism by which steroid solutions act to decrease pain in CTS patients is unclear.

It is most likely (can be speculated) that they cause changes in elements of sensitization in patients of CTS to cause analgesia, explained beyond their pharmacokinetic duration of action.

This improvement in sensitization may be more evident only in responders.
Selection Criteria

INCLUSION

Unilateral CTS Patients
Mild to Moderate severity
With symptoms predominantly involving
  Median nerve territory of the
  affected hand with or without
  proximal symptoms;
Both sensory and motor changes in EDx
Specifically,
(i) median nerve distal sensory latency
  of the index finger (43.60 ms);
  and/or
(ii) median nerve distal motor latency
  (44.20 ms)

EXCLUSION

Age > 65 yrs
Previous surgery or blocks
Other chronic pain conditions
Obvious primary cause of CTS such as
  hypothyroidism, pregnancy
Major psychological issues
Inability to communicate
Not consenting
Allergies to LA or steroid
Measurement of QST-Indicator of Peripheral Sensitization
Pressure Pain Threshold (PPT) as our study outcome

- QST-involves measuring the responses (i.e. non-painful sensations and pain) evoked by mechanical and thermal stimuli, intensity of which is controlled by automated devices.
- Advantage of QST would be the precision and quantification of sensory alterations.
- In CTS-it has been found that the PPT (pressure pain threshold-a marker for sensitization) was negatively associated with pain intensity and duration of symptoms.


Reasoning

Studies

- Gracely et al looked at 4 patients of chronic pain due to CRPS and neuroma with changes of mechanical hyperalgesia and allodynia. The symptoms-including sensitization markers, were eliminated or significantly decreased for the duration of local anesthetic blockade.
- Only one other study looks at such changes in patients who had painful arthritis and underwent hip replacement. The deep tissue hyperalgesia was evaluated before and 6-14 months after surgery.
Difference maps for CTS patients (baseline vs. postacupuncture) and healthy adults (baseline vs. 5 weeks later) for D2, D3, and D5 nonnoxious electrostimulation. Decreased fMRI activation was seen for D3 in CTS patients in contralateral SI, precentral gyrus, as well as the dorsolateral prefrontal and inferior parietal cortices. Differences for D2 and ulnar nerve innervated D5, as well as all three digits in healthy adults were less profound (cs: central sulcus).
Measurement of EMG findings
Study Outline

P=Carpal Tunnel Syndrome Patients
I=Steroid Injection
C=Local Anesthetic Injection
O=Success as determined through change in composite BCTQ
(success defined as improvement in BCTQ score of 0.8 or more)
T=at 1 month assessment

- **RCT: Randomized Controlled Study**
- **BCTQ: Boston Carpal Tunnel Questionnaire:** Disease-specific measure of self-reported symptom severity and functional status.
- **QST: quantitative sensory testing.** This can objectively calculate the threshold of pressure pain hyperalgesia and cold hyperalgesia (considered for this study).
- **fMRI; functional MRI.** Chronic pain changes the cortical representation of several areas of interest.
- **Edx:** Electrodiagnostic findings observed through electromyographic (EMG) testing of sensory and motor conduction related to median and ulnar nerves.
Variables Considered

**Subjective Evaluation**
- BCTQ evaluates both subjective symptom (SSS) and functional items (F status Scale)
- VAS-Visual analogue score indicates subjective pain intensity

**QST-Objective Indicator**
- The presence or absence of sensory findings of MECHANICAL AND THERMAL HYPERALGESIA
- The changes after injection can be quantified

**f-MRI-Objective Indicator**
- Can indicate the changes observed due to central sensitization in CTS patients.

**BCTQ**
- Anxiety Profile
- VAS scale for Pain (0-100)
- Duration of Pain
- Occupation

**EDx findings:** SNAP, SNCV, MNCV, comparative SNAP for Ulnar and Median

**QST tests:** Hypalgesia, Pressure Pain Threshold and Heat Pain Threshold

**f-MRI of Brain with Provocation Pain Manoeuvre**
**Null Hypothesis:** The proportion of patients with clinical success (defined as per the change in BCTQ) is equal or less in the steroid group as compared to the local anesthetic group.

Change according Boston CTQ-Primary Outcome at 1 month-**CATEGORICAL OUTCOME**
The threshold for success in BCTQ is a minimum change by 0.8 units or more.
PRIMARY OUTCOME # 2 QST changes

CTS

(LA) Local Anesthetic only

Within the patient change in BCTQ score (delta)
Observed as Pre and Post

LA + Steroid

Change (delta) as Mean and SD of the group

Compared as continuous variable

- It is difficult to categorise the response as Success or Failure as we do not have any THRESHOLD values to assume from previous studies.
- However the hypothesis is that all patients showing treatment success will demonstrate change in this outcome.
- The changes in mean between the 2 groups is assumed to result in significant difference; reflective of the clinical success.
PRIMARY OUTCOME # 3 f-MRI changes

It is difficult to categorise the response as Success or Failure as we do not have any THRESHOLD values to assume from previous studies.
However the hypothesis is that all/majority patients showing treatment success will demonstrate change in this outcome.
The mean difference between the 2 groups is assumed to result in significant difference; reflective of the clinical success.
**Sample Size Calculation:**

A Study with Similar Design as planned but without measurement of QST and MRI Changes-

- **Lidocaine (LA) Vs Steroid +LA**
- Response assessed at 1 month-primary outcome
- At 1 month 6 (20%) of 30 patients in the LA group had improved compared with 23 (77%) of 30 patients the intervention group (difference 57% (95% confidence interval 36% to 77%).

Our Sample Size Is Based On The Difference In Proportions Of Success In Each Treatment Arm.

Outcome Assessed: Change in composite BCTQ by 0.8 units or more (defined as success)

Control: 20%, Intervention: 70%.  
Alpha:0.05, Beta: 80%

N=number of patients needed in each arm=15

Primary Outcomes-assessment at 1 month

1. The proportion of patients with clinical success (defined as per the change in BCTQ) in the steroid group as compared to the local anesthetic group.

2. The mean change in f-MRI representative areas in steroid group as compared to local anesthetic group; compared as change from PRE-INJECTION to POST-INJECTION.

3. The mean change in PPT (pressure pain threshold) in steroid group as compared to local anesthetic group; compared as change from PRE-INJECTION to POST-INJECTION.

According to the estimation shown before, the calculated sample size is sufficiently powered to detect statistically significant changes for the stated categorical variable of success as defined by a change in BCTQ. The other 2 primary outcomes are continuous and the expected differences between the groups are assumed to be reflective of the success; we estimate that the sample size is sufficiently powered to detect such changes.
Secondary Outcomes-assessed at 3 months-at study completion

1. Change in VAS scores: Proportions of patients with decrease in VAS scores by 50%, between the 2 groups at 1 month and at 3 months.

2. Successful proportions of patients-defined by change in BCTQ at 3 months compared between LA and steroid group.

3. Subgroup Analysis of Magnitude of Change in f-MRI parameters (change in representative areas as mean ± SD) in successful patients compared to unsuccessful patients WITHIN THE 2 GROUPS.

4. Subgroup Analysis of Magnitude of Change in QST findings (change in threshold of PPT of CH-calculated as mean ± SD) in successful patients compared to unsuccessful patients WITHIN THE 2 GROUPS.

5. Correlation of change in BCTQ and f-MRI in individual patients.

6. Correlation of change in BCTQ and QST changes in individual patients.
1. Primary Outcome of Success between the 2 groups: Categorical using Chi Square
2. Primary Outcome of fMRI changes between the 2 groups: 2 way ANOVA before treatment and 3 way ANOVA after treatment.
3. Primary Outcome of QST changes between the 2 groups: 2 way ANOVA before treatment and 3 way ANOVA after treatment?
4. Correlation of change between BCTQ and fMRI or QST using spearman correlation test.
Study Design - Considerations and discussions?

**Analysis**

Expect analgesic failure; pursue analgesic success

Most analgesic drugs work well but in only a small percentage of people. Andrew Moore and colleagues argue that we need to move away from a focus on average response and seek out what works for each patient.

Andrew Moore professor¹, Sheena Derry senior research officer¹, Christopher Eccleston professor², Eija Kalso professor³

<table>
<thead>
<tr>
<th>Objective Change in Parameters</th>
<th>Subjective Outcome Reporting</th>
<th>Objective Change in Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in fMRI</td>
<td>Patient 1 - Steroid</td>
<td>Change in QST</td>
</tr>
<tr>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>✗</td>
<td>✗</td>
<td>✗</td>
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</tbody>
</table>

With this study any inference drawn about the treatment and resulting changes can be individually correlated to SUBJECTIVE and OBJECTIVE outcomes.
Study Implications

- Specific to CTS
  - Whether injection therapy works
  - Whether adding steroid has any benefit?
  - Whether the duration of relief is long lasting (3-6 months) in all responders or only in some?

In general

Does injection therapy really work in chronic pain patients who suffer from clearly demonstrable, objectively identifiable, compressive neuropathic pain conditions?

Why do only some patients respond? Are they the ones with sensitization and neuroplasticity which are more (easily) susceptible to therapeutic modifications (even temporary)?

Do they carry a separate **Neurosignature** as identified by f-MRI?
Challenges

- Obtaining Grants - financial consideration
- Recruitment: ?
Thanks
Example of QST changes with surgery in Osteoarthritis

<table>
<thead>
<tr>
<th></th>
<th>Before surgery (n = 14)</th>
<th></th>
<th>Following surgery (n = 12)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pain side</td>
<td>Contralat. side</td>
<td>Pain side</td>
<td>Contralat. side</td>
</tr>
<tr>
<td><strong>PPT (kPa)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>198.8 ± 22.7**†</td>
<td>252.8 ± 30.1</td>
<td>290.8 ± 44.7†</td>
<td>298.7 ± 52.7</td>
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<tr>
<td>Controls</td>
<td>338.7 ± 26.3</td>
<td>333.2 ± 22.0</td>
<td>333.8 ± 32.3</td>
<td>315.4 ± 29.8</td>
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<td><strong>LTT log 10 (mg)</strong></td>
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<tr>
<td>Patients</td>
<td>3.25 ± 0.4</td>
<td>3.11 ± 0.2</td>
<td>3.01 ± 0.3†</td>
<td>3.03 ± 0.2</td>
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<td>Controls</td>
<td>3.06 ± 0.2</td>
<td>3.00 ± 0.2</td>
<td>3.03 ± 0.3</td>
<td>2.97 ± 0.2</td>
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<tr>
<td><strong>CT (Δ °C)</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Patients</td>
<td>1.4 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Controls</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td><strong>WT (Δ °C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>2.5 ± 0.4*</td>
<td>3.0 ± 0.5*</td>
<td>3.8 ± 0.5†</td>
<td>3.8 ± 0.8†</td>
</tr>
<tr>
<td>Controls</td>
<td>4.2 ± 0.7</td>
<td>3.8 ± 0.5</td>
<td>3.2 ± 0.3</td>
<td>3.2 ± 0.3</td>
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<tr>
<td><strong>CT+WT (Δ °C)</strong></td>
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<tr>
<td>Patients</td>
<td>3.8 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>5.5 ± 0.7</td>
<td>5.6 ± 1.1</td>
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<tr>
<td>Controls</td>
<td>5.8 ± 0.9</td>
<td>5.4 ± 0.6</td>
<td>4.6 ± 0.4</td>
<td>4.8 ± 0.3</td>
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<tr>
<td><strong>HPT (°C)</strong></td>
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<td>Patients</td>
<td>41.2 ± 0.8</td>
<td>41.2 ± 0.7</td>
<td>43.1 ± 1.0</td>
<td>43.3 ± 0.9</td>
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<tr>
<td>Controls</td>
<td>42.9 ± 0.6</td>
<td>42.8 ± 0.8</td>
<td>42.8 ± 0.7</td>
<td>43.0 ± 0.6</td>
</tr>
</tbody>
</table>
This questionnaire evaluates two domains: (i) the functional status scale assesses ability to perform 8 common hand-related tasks; and (ii) the symptom severity scale includes 11 items assessing hand pain severity, numbness, and weakness at night and during the day.

Each question is answered on a 5-point scale (1 = no complaint; 5 = very severe complaint) with higher scores indicating greater severity.

The individual scores are summed and divided by the number of questions to give a final score for each scale (range, 1 to 5), with a higher score indicating a worse condition.

The BCTQ has established responsiveness, validity, and reliability. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire BMC Musculoskelet Disord. 2006; 7: 78.
Some examples of studies in literature supportive of a sample size power for fMRI and QST changes


   N=10 pts in each group, outcome at 20-30 mins after treatment.


   N=13 CTS and 12 controls


   N=12 pts and 14 controls