A Phase II Trial and Comparative Study on the Efficacy and Safety of Botox (Onabotulinumtoxin A) Injection Therapy for Carpal Tunnel Syndrome

Grace Van Hyfte

Western Michigan University
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Overview

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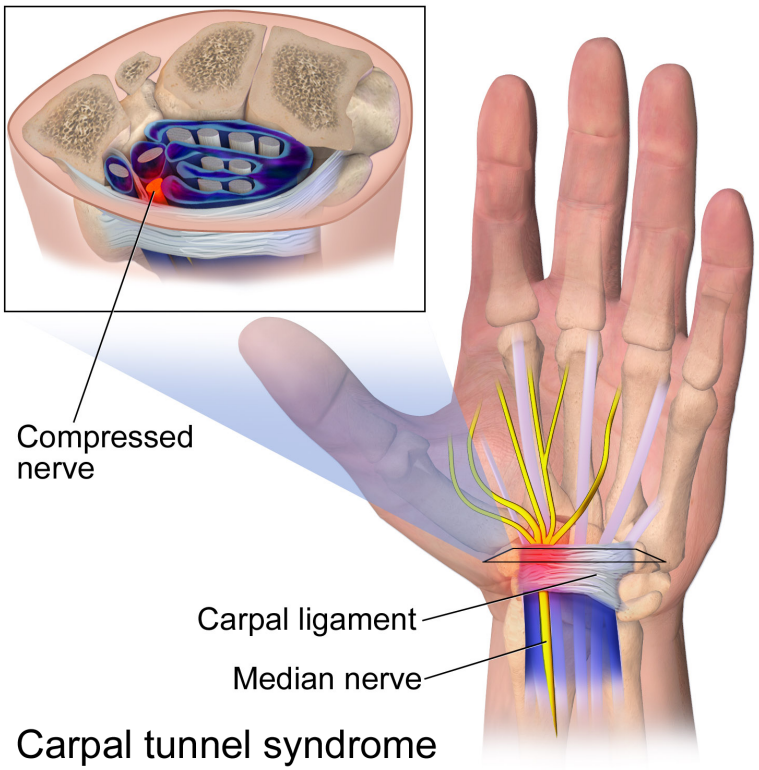
Carpal Tunnel Syndrome

The carpal tunnel is an osteofibrous canal in the wrist that serves as an enclosure space for the throughput of the median nerve [6]. Microtraumas to or compression of the median nerve via the carpal tunnel lead to nerve pain and swelling of the canal structure.

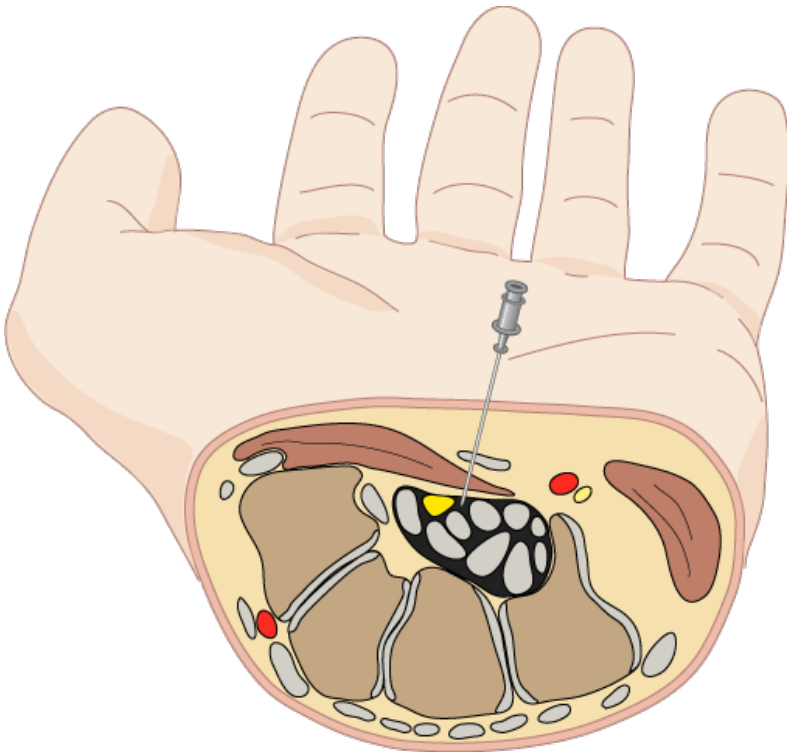


The Standard Therapy: Methylprednisolone

A common treatment for CTS is injectable corticosteroids near the carpal tunnel to reduce inflammation and tunnel pressure [5]. Negative side effects in the Methylprednisolone family[4]:

- weight gain
- worsening diabetic conditions
- high blood pressure
- potassium loss

Goal: Find an alternative treatment for individuals with CTS and additional health conditions where steroid use is a health risk.



The Experimental Drug: Onabotulinumtoxin A

The botulinum toxin produced by the bacterium Clostridium botulinum has been used extensively in cosmetic treatments, and has been shown to relieve headaches, chronic pain, and different types of neuropathic pain [7].

Modus operandi: blocks nerve signalling for muscle contraction when injected locally

Study Intent: To determine if the physiological effects of botulinum toxin (Onabotulinumtoxin A) can effectively reduce inflammation and alleviate the symptoms of CTS.

Overview

Objectives

Primary

Conduct a Safety and Activity (SA) trial to evaluate the effect of Onabotulinumtoxin A on clinical symptoms

- **Safety**:
  - To evaluate the safety, tolerance, and identify adverse outcomes/effects of the treatment.
- **Efficacy**:
  - To evaluate the effect of Onabotulinumtoxin A as measured by a $\geq$30% improvement in the Jamar Pinch gauge tests.
  - To evaluate the effect of Onabotulinumtoxin A as measured by a $\geq$20% reduction in median nerve cross-sectional area in a neuromuscular ultrasound.
  - To evaluate the effect of Onabotulinumtoxin A as measured by a $\geq$15% reduction in Distal Motor and/or Sensory Latency

Secondary

Comparative study to evaluate the efficacy of Onabotulinumtoxin A on clinical symptoms as compared to the standard medical treatment, Methylprednisolone.

Exploratory Objectives

Exploratory

- To evaluate the effect of Onabotulinumtoxin A from baseline as measured by Levine Symptom Severity Scale (SSS) severity scores.
- To evaluate the effect of Onabotulinumtoxin A from baseline as measured by Levine Function Severity Scale (FSS) severity scores.
- To evaluate the effect of Onabotulinumtoxin A compared to Methylprednisolone as measured by Levine Symptom Severity Scale (SSS) severity scores.
- To evaluate the effect of Onabotulinumtoxin A compared to Methylprednisolone as measured by Levine Function Severity Scale (FSS) severity scores.

Overview

Study Population

- Michigan
- Neurology and affiliated centers (multi-center)
- Informed, voluntary basis through participating physicians
- 25 in SA trial + 60 in comparative study for a total of 85 subjects

Inclusion Criteria

- ✓ Adults between the ages of 18 and 60 at start of enrollment
- ✓ Confirmed idiopathic Carpal Tunnel Syndrome diagnosis by a medical doctor at $\leq$ 50 years of age
- ✓ On-staff doctor confirms idiopathic CTS during initial screening
- ✓ CTS symptom duration for at least 3 months with poor response to wrist splinting

Criteria to be assessed during Baseline Phase and prior to Randomization

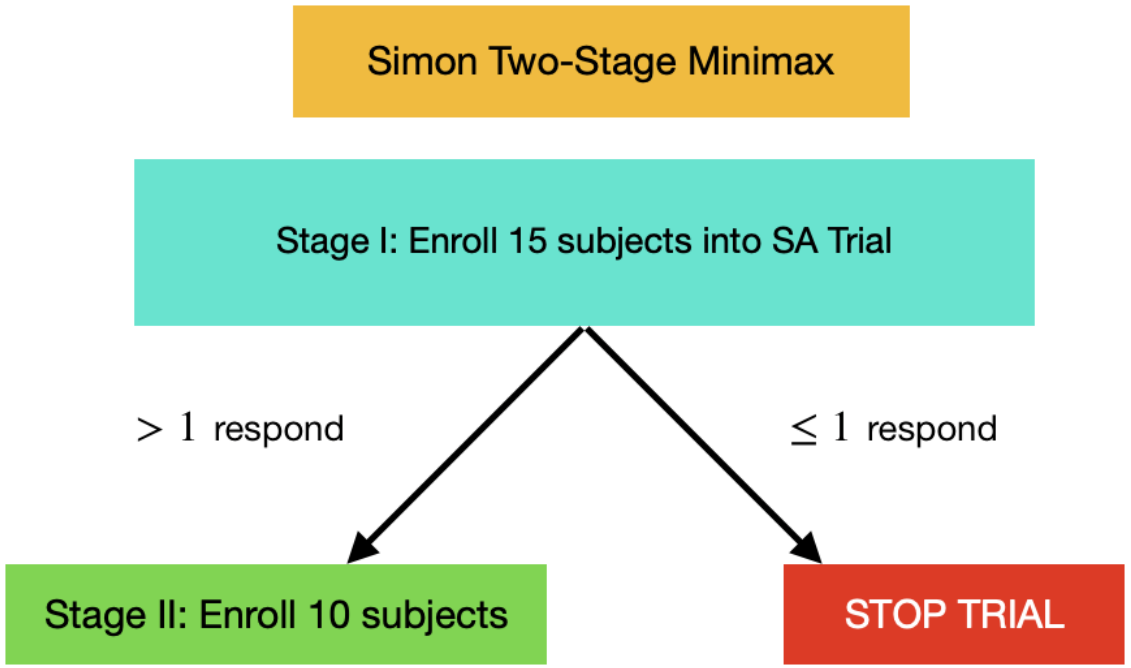
- ✓ Median nerve cross-sectional area (CSA) $\geq 11mm^2$ as indicative by neuro-muscular ultrasound
- ✓ Median Nerve Distal Sensory Latency (DSL) $\geq$ 2.2 ms measured by electrodiagnostic oscilloscope [2]
- ✓ Median Nerve Distal Motor Latency (DML) $\geq$ 3.5 ms measure by electrodiagnostic oscilloscope

Exclusion Criteria

- ✗ Patients with prior carpal tunnel surgery
- ✗ Previous steroid or Botox injection to treat CTS or otherwise
- ✗ Allergies to any of the active or inactive ingredients in Onabotulinumtoxin A or Methylprednisolone
- ✗ Prior diagnosis of a Neuromuscular Junction disorder [7]
- ✗ Currently pregnant or breastfeeding
- ✗ Prior diagnosis of any form of diabetes mellitus
- ✗ Known abuse of drugs and/or alcohol [1]
- ✗ Severe medical illness

Overview

Safety and Activity Trial



H_0: The true response rate $p_0 = 0.10$
H_1: The true response rate $p_1 = 0.30$
The null hypothesis will be rejected if 6 or more responses are observed in 25 subjects. This design yield a Type I error rate of 0.038 and power of 0.8017 when the true response rate is 0.30.

Comparative Study

- 1mL suspension of 40mg Methylprednisolone; carpal tunnel
- 40 units Onabotulinumtoxin A; opponens pollicis and abductor pollicis brevis
- Triple-blind (Subjects, Investigators, Outcome Assessors
- Block Randomization of 60 Subjects
  - 10 blocks
  - Block size $= 6$

Block Randomization example:
ABABBA, ABABAB, BBBAAA, ... etc.

- 20 total permutations
- Random number selection $[1, 20]$ with replacement

Subject	Block 1	Treatment
1	A	Onabotulinumtoxin A
2	B	Methylprednisolone
3	A	Onabotulinumtoxin A
4	B	Methylprednisolone
5	B	Methylprednisolone
6	A	Onabotulinumtoxin A

Table: *Example Block Randomization for Permutation 'ABABBA'*

Study Schedule

Phase II: Onabotulinumtoxin A Study Schedule

	Enrollment	Evaluation	Baseline week 1 t= -2	Baseline week 2 t= -1	Allocation t=0	Follow-up t= 1 (at 3wks)	Follow-up t= 2 (at 6wks)	Follow-up t= 3 (at 9wks)	Follow-up t= 4 (at 12wks)	Closing Phone Interview t= 5 (at 16wks)
Enrollment	X									
Informed Consent	X									
Eligibility Screening		X								
Randomi-zation					X					
Intervention										
SA Trial						—	—	—	—	—
Obotulinum-toxin A										
Methyl-prednisolone										
Assessment										
Levine SSS			X	X						
Levine FSS			X	X						
Jamar Pinch Gauge			X							
Neuro-muscular Ultrasound			X							
Electro-diagnostics DSL										
Electro-diagnostics DML			X							

Overview

Neuromuscular Ultrasound

Median nerve cross-sectional area (CSA)
Normative range $\approx 9 - 12mm^2$
CTS individual CSA range is larger

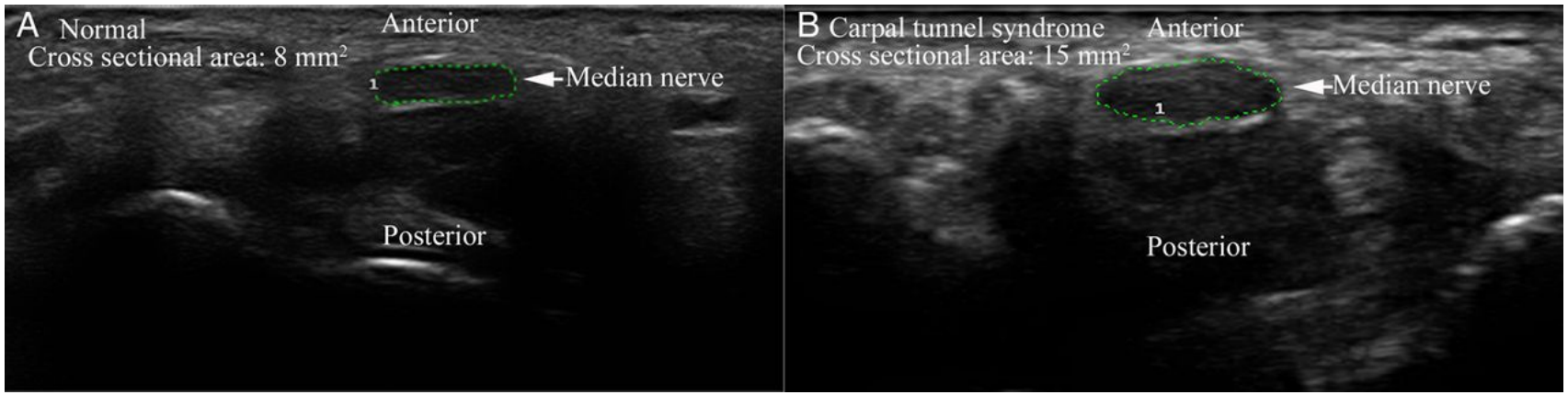


Figure: Neuromuscular Ultrasound of Median Nerve CSA

Electrodiagnostics

Nerve conduction studies (NCS) to measure the Distal Sensory Latency (DSL) and Distal Motor Latency (DML).
Latency: conduction speed (ms) measured as the interval between nerve stimulation of a muscle and the observed response.

- Normative DML $\approx$ 3ms, DSL $\approx$ 2ms
- CTS individuals experience longer latencies

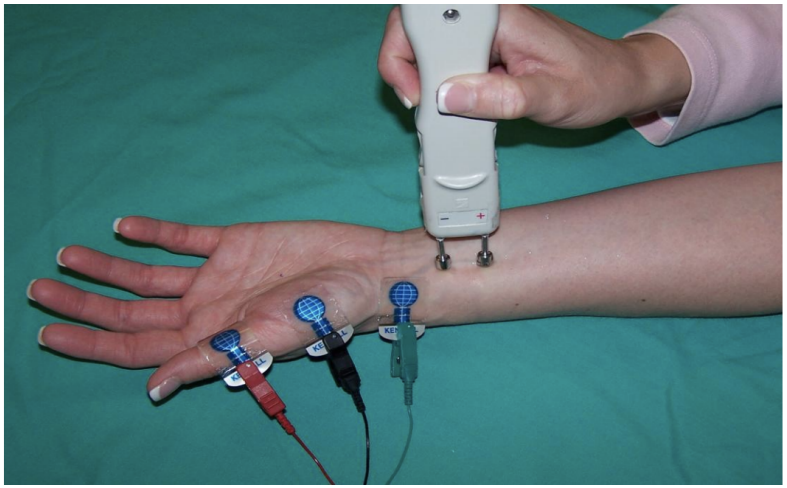


Figure: Nerve Conduction Study on the Median Nerve

Dynamometer and Jamar Pinch Gauge

Three maximum strength attempts (45min intervals)
Three endurance strength attempts (30s intervals)

- CTS individuals experience greater fatigue
- Maximum strength during stress action weakened by CTS

Figure: Jamar Dynamometer Device

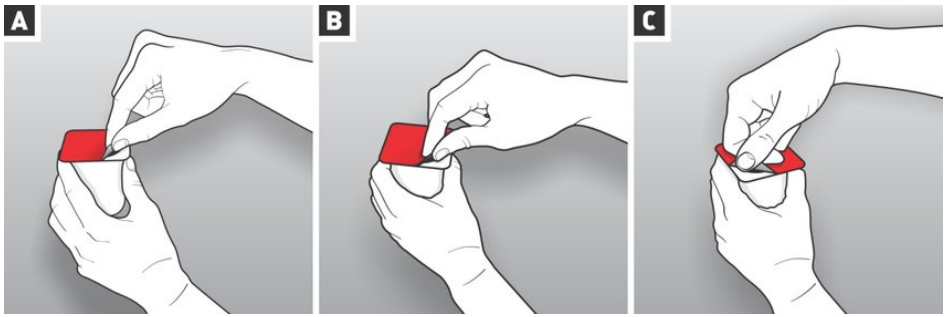


Figure: A. Pulp, B. Chuck (3-finger), C. Lateral

Levine Symptom and Function Severity Survey

The Levine Symptom and Function Severity Scale questionnaires are based on a multiple-choice question and answer format, in which each answer has a score value [3]. The "severity" rating is based on the average score value from the questionnaire.

The Symptom Severity Scale

1. How severe is the hand or wrist pain that you have at night?	6. Do you have numbness (loss of sensation) in your hand?
1 I do not have hand or wrist pain at night	1 No
2 Mild pain	2 I have mild numbness
3 Moderate pain	3 I have moderate numbness
4 Severe pain	4 I have severe numbness
5 Very severe pain	5 I have very severe numbness
2. How often did hand or wrist pain wake you up during a typical night in the past two weeks?	7. Do you have weakness in your hand or wrist?
1 Never	1 No weakness
2 Once	2 Mild weakness
3 Two or three times	3 Moderate weakness
4 Four or five times	4 Severe weakness
5 More than five times	5 Very severe weakness

Figure: Levine Symptom Severity Scale Survey Sample

Overview

Statistical Methods

SAS statistical software will be used for the following types of analyses:

- Descriptive Statistics
- Mean and Standard Deviations (for all assessments)
- Paired t-Test (SA trial: pre- vs. post-treatment response)
- Independent Samples t-Test (comparative study: Onabotulinumtoxin A vs. Methylprednisolone)

References

Hofer M. Ranstam J. Atroshi I. Flondell M. "Steroid Injection Treatment of Carpal Tunnel Syndrome". In: *Region Skane* (2008). https://clinicaltrials.gov/ct2/show/NCT00806871?type=Intrcond=%22Carpal+Tunnel+Syndrome%22phase=14draw=2rank=20.

Kemble F. "Electrodiagnosis of the carpal tunnel syndrome". In: *Journal of Neurology, Neurosurgery, and Psychiatry* 31 (1968). https://jnnp.bmj.com/content/jnnp/31/1/23.full.pdf, pp. 23–27.

Wim AB Stalman Daniëlle AWM van der Windt Marinda N Spies-Dorgelo Caroline B Terwee. "Reproducibility and responsiveness of the Symptom Severity Scale and the hand and finger function subscale of the Dutch arthritis impact measurement scales (Dutch-AIMS2-HFF) in primary care patients with wrist or hand problems". In: *Health Qual Life Outcomes* 87 (2006). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1660574/#: :text=This%20questionnaire%20contains%20eleven%20questions,clinical% pp. 299–303. DOI: 10.1186/1477-7525-4-87.

Omudhome Ogbru. "methylprednisolone (Medrol)". In: *MedicineNet* (). https://www.medicinenet.com/methylprednisolone/article.htm.

Institute for Quality and Efficiency in Health Care (IQWiG). "Carpal tunnel syndrome: How effective are corticosteroid treatments?" In: (2017). https://www.ncbi.nlm.nih.gov/books/NBK279598/#: :text=Injecting%20corticosteroids%20near%20the%20carpal,been%20tested%20ir

S. Alashkar Ahmed A Elsharkawy Shymaa A Hablas W. Nada. "The effect of botulinum toxin type A injection in decreasing intratunnel tendon tension in carpal tunnel syndrome: a randomized controlled trial for efficacy and safety". In: *Egyptian Rheumatology and Rehabilitation* 46 (2019). http://www.err.eg.net/article.asp?issn=1110-161X;year=2019;volume=46;issue=4;spage=299;epage=303;aulast=Hablas, pp. 299–303. DOI: 110.4103/err.err_35_19.

PLLC. Sucher B. Arizona Arthritis Rheumatology Research. "BOTOX® (Onabotulinumtoxin A) Injection(s) as a Treatment for Carpal Tunnel Syndrome". In: (2014). https://clinicaltrials.gov/ct2/show/NCT02070302?type=Intrcond=%22Carpal+Tunnel+Syndrome%22phase=14draw=2rank=9.