

# Utilizing Platelet-Rich Plasma as an Adjuvant to Carpal Tunnel Release for Severe Carpal Tunnel Syndrome

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## 1. PURPOSE OF THE STUDY

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### a. Brief Summary

This study assesses the potential benefit of adjuvant platelet-rich plasma (PRP) with carpal tunnel release (CTR) for patients with severe carpal tunnel syndrome (CTS). CTR is a rather common procedure performed and seems to be quite effective for those with moderate CTS, but a number of patients with severe CTS do not have quite the same response post-CTR. We will recruit patients who fall into the severe CTS category and compare CTR with and without adjuvant PRP to see if PRP can improve outcomes of this common surgery.

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### b. Objectives

Our primary aim of the project is to compare the post-CTR outcomes of patients with severe CTS with and without adjuvant PRP. We hypothesize that patients with severe CTS that undergo CTR with adjuvant PRP will have significantly improved Boston Carpal Tunnel Questionnaire (BCTQ) scores and grip strength in the long-term when compared to those with severe CTS that undergo CTR without adjuvant PRP.

We hope that this study will provide evidence that PRP can be used as an effective adjuvant treatment for those with severe CTS that undergo CTR who have not traditionally had the best post-operative results. In particular, this will add to the field of evidence for PRP being used in nerve regeneration that is currently scant. This could open up doors for many other utilizations of PRP for peripheral nerve injuries within sports medicine.

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### c. Rationale for Research in Humans

The purpose of this study is to assess adjuvant PRP with CTR in patients with severe CTS. There are previous studies looking at the role of PRP in nerve regeneration at the basic science and animal model levels, but there are few-to-no studies that investigate it in humans. Human studies are thus required to assess this purpose.

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## 2. STUDY PROCEDURES

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### a. Procedures

1. Study team recruits patients with severe CTS who meet inclusion and exclusion criteria in an outpatient hand surgery clinic. Patient will be consented by the research team if they agree to participate in the research study.
2. This will be a single blinded study, and participants will have an equal chance to be placed in either group. Participants will be randomized using permuted block randomization predetermined by our dedicated orthopedic biostatistician into two study groups: those that undergo CTR with adjuvant intra-operative PRP and those that undergo CTR without adjuvant PRP. All participants will have a pre-operative electromyography/nerve conduction study (EMG/NCS).
3. Primary outcome measures (BCTQ and grip strength), and secondary outcome measures (PROMIS; 2 point discrimination - thumb, index finger and middle finger; key pinch; 3 finger pinch; and EMG/NCS results) will be collected and stored in REDCap at initial visit. BCTQ and PROMIS will actually be available online for patient to complete at his/her convenience.
4. Patients will undergo CTR with or without adjuvant PRP (based on assigned study group). They will not know which group they are in (single blinded).
5. BCTQ and PROMIS will be collected online at 3 months and 6 months post-operatively. EMG/NCS will be performed pre-operatively, at 6 month post-operatively in the Sports Medicine clinic. At this visit, we will also collect data on 2 point discrimination, grip strength, key pinch, and 3 finger pinch.
6. We will store data in REDCap.
7. Data will be analyzed with the assistance of our biostatistician, and results will be written up.

We will also be borrowing a centrifuge machine from Factor Medical, the company providing the Selphyl PRP kits. The machine will be used in conjunction with the PRP kits to derive the PRP.

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### b. Procedure Risks

The research procedures are optimized to be the least risky that can be performed with sound research design. CTR is a standard treatment for those with severe CTS, and numerous studies have looked into PRP as non-operative treatment for mild to moderate cases of CTS with some promising results and few negative side effects reported. Thus from previous studies, this investigation involves the least risky procedures while also advancing the science behind PRP.

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### c. Use of Deception in the Study

No deception will be used in the study. Patients will be notified of the two possible treatment groups they will be assigned to prior to consenting.

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### d. Use of Audio and Video Recordings

No audio or video recording will occur.

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**e. Alternative Procedures or Courses of Treatment**

Alternative courses of treatment and procedures include conservative management with bracing, hand therapy, and steroid injections. However, once patients have reached the severe form of CTS that we are recruiting, standard treatment is CTR unless there is a surgical contraindication.

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**f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?**

Yes. Conclusion of this study does not preclude the patients from further treatment including repeat surgery in the future.

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**g. Study Endpoint(s)**

We can analyze the data after each of the collection points during the study. However, since it will be continuous enrollment, each of the participants will be at different stages of the study procedure at any one time point. It would be reasonable to look at outcomes after half of the target sample size (aiming for 46 total participants) has had their 6 month post-operative data collected). If one treatment proves to be clearly more effective than the other during the course of the study (although this is unlikely given required statistical sample size), we could terminate the study prior to enrolling the projected total participant population. Otherwise the study will continue until we have reached our target sample size of 46 (23 in each group) that is based on our power calculation to achieve statistical significance. We approximate that the recruitment period will be about 3 years.

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**3. BACKGROUND**

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**a. Past Experimental and/or Clinical Findings**

CTS is the most common peripheral nerve entrapment and affects approximately 3% of the general population. Clinical symptoms include pain, numbness, tingling, and weakness in the hand innervated by the median nerve. Although CTS is a clinical diagnosis, EMG/NCS is traditionally used to categorize CTS into mild, moderate, and severe. Mild and moderate cases of CTS can often be treated with conservative measures including splinting, hand therapy, and steroid injections. Moderate cases that do not respond to conservative treatment as well as severe cases typically require surgical management with CTR. CTR seems to be quite effective for those with moderate CTS without axonal loss, but many of those with severe CTS with axonal loss on EMG/NCS do not necessarily respond well even after surgery.

Over the past decade, regenerative medicine techniques have been increasingly utilized in the treatment of musculoskeletal disorders. PRP is one of the first and most studied regenerative medicine techniques. It activates cell proliferation by concentrating platelets and growth factors and creating an environment for healing. There have been some studies on utilizing PRP to promote nerve regeneration, but these have been primarily in the basic science and animal model realms. PRP has been studied in treating mild to moderate CTS non-operatively with promising results that suggest a role in nerve regeneration. Thus, PRP can be considered as a potential adjuvant treatment to CTR for severe cases of CTS that may otherwise not respond well to CTR alone.

To date, there is only one study (by Trull-Ahuir et al. in Scientific Reports - Nature Research) that looked at this specific topic. However, our study will differ in numerous ways. First, we will have a control group (Trull-Ahuir et al. had compared PRP versus PPP). Also we plan to perform longer term follow-up up to 6 months. Our outcome measures will include more objective data such as repeat EMG/NCS. Additionally, we plan to focus on only those with severe CTS since it is the group that has a relatively poor prognosis even with surgical release.

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**b. Findings from Past Animal Experiments**

There have been previous studies looking at PRP's effect in peripheral nerve regeneration in rat models (Kucuk et al. in Acta Orthop Traumatol Turc) and in rabbit models (Ikumi et al. in Microsurgery). Both studies demonstrated positive effects of PRP on nerve regeneration. This has led us to attempt to further investigate these positive effects in humans.

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**4. RADIOISOTOPES OR RADIATION MACHINES**

N/A

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**5. DEVICES USED IN THE STUDY**

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**a. Investigational Devices (Including Commercial Devices Used Off-Label)**

N/A

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**b. IDE-Exempt Devices**

IND-Exempt Device 1	
Name:	PRP Kit (Selphyl)
Description:	Platelet-Rich Plasma (PRP) Kit - Utilized to derive PRP from subject's own blood.

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**6. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY**

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**a. Investigational Drugs, Biologics, Reagents, or Chemicals**

N/A

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**b. Commercial Drugs, Biologics, Reagents, or Chemicals**

Commercial Product 1	
Name:	Platelet-Rich Plasma

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**7. DISINFECTION PROCEDURES FOR MEDICAL EQUIPMENT USED ON BOTH HUMANS AND ANIMALS**

N/A

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## 8. PARTICIPANT POPULATION

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### a. Planned Enrollment

- (i) We expect to enroll 46 participants at the Stanford-affiliated site.
- (ii) Our study is single-site, so 46 will remain the expected total number of participants.
- (iii) Participants will all be adults aged 18 years and older seen in the outpatient hand surgery clinic who are diagnosed with severe CTS.

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### b. Age, Gender, and Ethnic Background

The participant population will consist of adults aged 18 years and older seen in the outpatient hand surgery clinic who are diagnosed with severe CTS based on EMG/NCS criteria. The participant population may have a small predominance of females over males as in previous studies, females have had a slightly greater incidence of CTS than males. Ethnic backgrounds of the participant population are currently unknown.

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### c. Vulnerable Populations

No potentially vulnerable subjects will be enrolled in our study. Women and minorities will be included, but treatment of their condition and participation in the study will not be predicated based on their volunteering in the study. All patients will receive the standard of care even if they do not participate in the study, and there are no financial incentives to persuade those who are economically disadvantaged to participate in the study.

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### d. Rationale for Exclusion of Certain Populations

Children are not included in the study as CTS is rarely found in this population.

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### e. Stanford Populations

We do not plan for there to be any study participants who are laboratory personnel, employees, and/or students.

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### f. Healthy Volunteers

There will not be any healthy volunteers as the inclusion criteria requires that the participants have severe CTS.

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### g. Recruitment Details

The study team will chart review EMG/NCS studies performed in the Sports Medicine clinic weekly and provide a list to the Hand Surgery providers of the patients that meet inclusion/exclusion criteria. In the Hand Surgery clinic, the patients will be provided information on the study and be consented if he/she decides to participate.

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### h. Eligibility Criteria

#### i. Inclusion Criteria

To be included in the study, participants must meet the following criteria:

1. Adult age 18 years and up.

2. Diagnosed with severe CTS based on EMG/NCS, meaning those with evidence of axonal loss (absent or low amplitude median sensory nerve action potential and/or absent or low amplitude median motor nerve action potential and/or evidence of abnormal spontaneous activity, reduced recruitment, or motor unit action potential changes on needle EMG of median innervated muscles).

ii. Exclusion Criteria

Study participants will be excluded if they meet the following criteria:

1. Younger than age 18 years (minor status).
2. Diagnosed with concomitant peripheral neuropathy.
3. Previous CTR on the affected side.
4. Have contraindications to PRP (platelet dysfunction syndrome, critical thrombocytopenia, hemodynamic instability, septicemia, local infection at site of procedure, consistent use of NSAIDs within 48 hours of procedure, steroid injection at treatment site within 1 month, systemic use of steroids within 2 weeks, tobacco use, recent fever or illness, or cancer).

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**i. Screening Procedures**

1. All potential participants will have a pre-operative EMG/NCS performed. Based on the EMG/NCS results, the research team will speak to those patients who qualify during their normally scheduled office visit regarding their interest in participating in the study.
2. The patients who volunteer to participate will be consented in clinic. If the patient would like some time after the office visit to think about it, the research team may consent the patient over email if the patient decides to proceed with the study.

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**j. Participation in Multiple Protocols**

The first question on the consent form asks the participant if they are participating in any other research studies. We do not plan on having participants enrolled in multiple studies at the same time, and if they are already enrolled in another study, we will ensure that those study protocols would not affect ours prior to consenting.

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**k. Payments to Participants**

Research participants will not be paid to participate in the study. All data will be collected during the typical office visits that patients who undergo CTR have even outside of this study.

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**l. Costs to Participants**

PRP kits will be donated from a vendor, so there are no additional costs for the participants in the study.

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**m. Planned Duration of the Study**

The duration of the entire study will likely be from 3/1/2021 to 2/28/2024. We anticipate that it will take approximately 3 years to recruit our desired sample size of 46 participants based on our power calculation to detect minimally clinically important differences in our primary outcome measures. Analysis of the data can be ongoing throughout the data

collection process, but we should have all of our 6 month data by 2/28/2024. Then the data can be written up.

(i) We estimate that screening of a participant should take about 5 minutes during the office visit.

(ii) Subjects will be required to have additional visits in the Sports Medicine clinic at 6 months post-op for quick repeat EMG/NCS's. Otherwise, there is no significant increased time in terms of active participation in the study for the patient.

(iii) Analysis of participant data will take approximately 4 weeks following the completion of data collection.

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## 9. RISKS

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### a. Potential Risks

#### i. Investigational devices

There are no investigational devices in this study.

#### ii. Investigational drugs

Not applicable.

#### iii. Commercially available drugs, biologics, reagents or chemicals

There has been increasing evidence on PRP's use for musculoskeletal conditions, but the majority of the evidence is on knee osteoarthritis and chronic tendinopathies. Based on these previous studies, the primary risks include local infection (<1% chance) and pain at the site which are also risks of CTR alone.

#### iv. Procedures

Risks associated with the CTR include bleeding, local infection, increased pain, damage to the median nerve and/or surrounding structures, and risks associated with anesthesia. Major complications such as nerve damage occur in <1% of cases. Blood draws for the PRP also have risks of bleeding and infection but are very commonly done with rare complications. Risks associated with EMG/NCS include bleeding, local infection, and discomfort during the test. Bleeding and infection occur in <1% of tests performed.

#### v. Radioisotopes/radiation-producing machines

There are no radioisotopes/radiation-producing machines involved in this study.

#### vi. Physical well-being

The major risks to physical well-being for participants in the study involve those mentioned above associated with CTR, PRP, and EMG/NCS.

#### vii. Psychological well-being

There are no risks to the psychological well-being for participants in the study.

#### viii. Economic well-being

There are no direct risks to the participants' economic well-being as there are no additional costs to them during the study.

ix. Social well-being

There are no risks to the social well-being for participants in the the study.

x. Overall evaluation of risk

Low

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**b. International Research Risk Procedures**

N/A

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**c. Procedures to Minimize Risk**

All participants will be notified of potential risks of the study that, as outlined above, are primarily related to CTR and PRP. Patients will be followed longitudinally in one of the investigator's outpatient hand surgery clinic, and all adverse events will be recorded and monitored. To minimize risks to the confidentiality of identifiable information, participants will be assigned a study ID number, and all data will be stored securely in REDCap. Only the research team at Stanford will have access to the data.

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**d. Study Conclusion**

The experiment will terminate for each patient following the 12 month follow-up visit. Those who decide to receive other interventions within these follow-up windows will have these interventions noted in our data. Necessary medical and professional intervention will be available through the clinic for adverse events as these will all be patients of one of the investigators.

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**e. Data Safety Monitoring Plan (DSMC)**

i. Data and/or events subject to review

Adverse events related to CTR with or without PRP as well as protocol deviations such as variation from post-operative standard of care will be reported and monitored throughout the study.

ii. Person(s) responsible for Data and Safety Monitoring

The protocol director and study team will be responsible for Data and Safety Monitoring for this study.

iii. Frequency of DSMB meetings

N/A

iv. Specific triggers or stopping rules

If there are 2 or more SAEs reported that are deemed related to the adjuvant PRP, this will trigger evaluation by the study team to determine whether it is safe to continue

the study. Otherwise the study will end once the target sample size of 46 patients has been reached.

v. DSMB Reporting

The PD will disseminate the outcome of the reviews to the IRB and the study sponsor if reviews related to SAEs are required during the study.

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

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**f. Risks to Special Populations**

N/A

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**10. BENEFITS**

Participants who are in the adjuvant PRP group may experience enhanced improvement in CTS symptoms if our hypothesis proves correct. In terms of the knowledge acquired from this study, we hope that this study will provide evidence that PRP can be used as an effective adjuvant treatment for those with severe CTS that undergo CTR who have traditionally had a relatively poor prognosis even with surgical release. This will add to the field of evidence for PRP being used in nerve regeneration that is currently scant and could open up doors for many other utilizations of PRP for peripheral nerve injuries within sports medicine.

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**11. PRIVACY AND CONFIDENTIALITY**

Patient recruitment and consent will primarily be completed in person in clinic. In the cases where the patient decides to participate following their office visit and consent is obtained via email, we will utilize secure mail through Stanford and limit transmission of information to the consent form.

PHI and HIPAA identifiers to be collected in this study include name, date of birth, gender, ethnicity, handedness, date of surgery, medical comorbidities, questionnaire results, EMG/NCS data, and physical exam data including grip strength and 2 point discrimination.

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.