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14. ABSTRACT
Spinal cord injury (SCI) is the result of damage to the spinal cord either due to trauma (90% of cases) or disease (eg. Cancer). This is typically a devastating injury, leaving many patients with permanent disability. Despite advances in acute patient management, patients with SCI are two to five times more likely to die prematurely than those without SCI. More than 50% of the 11-12,000 new SCIs that occur in the United States each year involve the cervical spine resulting in diminished or complete loss of arm and/or hand function. Cervical SCI patients consistently rank hand function as the most desired function above bowel and bladder function, sexual function, standing, and pain control. The *overall goal* of the proposed study is to evaluate the efficacy of nerve transfers to treat patients with cervical SCIs. Over the last decade, nerve transfers have been used with increasing frequency to treat peripheral nerve and/or brachial plexus injuries. Nerve transfers involve the transfer of nerve function that is less critical and/or redundant to a more critical area of motor function. Recently, these same principles used to treat peripheral nerve injuries have been applied to patients with SCIs, with promising early results. Using uninjured nerve above the level in the spine where the injury occurred, nerve transfers can provide improved upper extremity and hand function to veterans and patients living with cervical SCIs. Since nerves below the injured segment of spine are still in continuity with the distal muscle targets (i.e. hand), they remain receptive to reinnervation even years after SCI.

15. SUBJECT TERMS
None listed.

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1. INTRODUCTION:

Spinal cord injury (SCI) is a significant public health problem with approximately 12,000 new cases each year. More than 50% of SCIs occur in the cervical spine (i.e., tetraplegia), resulting in some loss of arm and/or hand function. Nerve transfers to treat brachial plexus and peripheral nerve injuries have gained significant momentum over last decade. The central principle of nerve transfers is the conversion of a high level nerve injury, to a low injury, placing regenerating axons in close proximity to the target end-organs. While tendon transfers have an established role in the management of patients with SCI and tetraplegia, only recently have nerve transfers been considered as a potential treatment option in patients with cervical SCIs. Utilizing donor nerves above the SCI, nerve transfers can be done either subacutely into the zone of the injury (upper and lower motor neuron dysfunction) or in a delayed fashion below the zone of injury. Motor neurons in the zone of injury are subject to lower motor degeneration, with a similar degeneration pattern seen in peripheral nerve injuries. Injuries in the zone of injury should be treated aggressively, to prevent progressive motor endplate fibrosis and contractures. Motor neurons below the level of injury are still in continuity with distal motor endplates, these nerves do not undergo typical Wallerian degeneration as observed in the zone with injury. This provides two distinct windows of opportunity for subacute treatment (< 6 months) after injury and chronic treatment (years) after injury. The long-term objective of this proposal is to establish and validate clinical guidelines on the use of nerve transfers to restore distal motor function following a cervical SCI. Central Hypothesis: Peripheral nerve transfers in patients with cervical spinal cord injury will improve distal motor function, functional independence, and patient quality of life. A prospective single institution non-randomized single arm design will be utilized. Twenty consecutive subjects with cervical ASIA A-B (International Standards for Neurological Classification of Spinal Cord Injury) SCI and hand function impairment who fit the International Classification for Surgery of the Hand 0-4 will be identified. Primary Outcome Measures: Upper motor strength. (Manual motor testing & Hand Held Dynamometry) Secondary Outcome Measures: Disabilities of the Arm, Shoulder, and Hand (DASH), Michigan Hand Questionnaire (MHQ), Short Form 36 (SF-36) rates of intraoperative and post-operative complications, and rates of reoperation. (pre-operative, post-operatively - 6, 12, 18, 24, and 36 months). We believe this study will provide substantial benefit to patients enrolled at our institution and expect the results to support a larger multi-institutional phase III clinical trial.

2. KEYWORDS:

Spinal cord injury, nerve transfer, quality of life, upper extremity function, subacute

3. ACCOMPLISHMENTS:

1. Finalize clinical protocol
2. Develop informed consents
3. Develop case report forms
4. Obtain required licensing agreements for electronic outcome assessments
5. Submit documents to Washington University IRB and obtain approval
6. Submit documents to USAMRMC and HRPO and obtain approval
7. Recruit full time study coordinator
8. Recruit hand therapist
9. Establish mechanism for patient identification and recruitment

What was accomplished under these goals?

Major Task 1: Coordinate patient recruitment

Milestones achieved: We have identified several potential referral sites and have established a strong referral source through our local rehabilitation hospital. Ongoing outreach efforts remain in place to maintain ongoing referrals for our phase II trial.

Major Task 2: Coordinate study staff for clinical trial

Milestones achieved: Our dedicated hand therapist Anna VanVoorhis continues to perform all post-operative hand assessments, last year she joined our team on a 20% effort to allow ongoing and reliable therapy to patients as the study transitions to a follow-up component. She continues to provide ongoing hand therapy to all post-operative patients on a regular basis along with objective post-operative assessments. In addition, she has educated several regional hand therapists in appropriate post-operative therapy to allow patients to get appropriate therapy closer to home. Our research coordinator Linda Koester continues to facilitate follow-up assessments by the PI and Co-PI. Those patients that have been enrolled continue to receive coordinated care to ensure all scheduled follow-up visits are maintained.

Major Task 3: Participant recruitment, therapy, participant evaluation

1. *Milestones Achieved:* We have enrolled 20 patients since study initiation, with one patient withdrawal (Patient 20/20) prior to operative intervention and one patient death (Patient 13/20) approximately nine months following surgery, unrelated to surgical intervention. Details on each enrolled patient are as follows: The first patient treated was a C6 ASIA A/IC3: that underwent transfer of the supinator to the PIN, Axillary to triceps, and brachialis to AIN. The second patient is a C8/IC4: underwent transfer of the brachialis to AIN and MABC to ulnar sensory. The third patient was a C3 ASIA A/IC0: underwent transfer of the spinal accessory to musculocutaneous nerve and playtsma motor branch to triceps. The forth patient is a C5 ASIA A/IC2: underwent bilateral supinator to the PIN and brachialis to AIN. The fifth patient was a C4 central cord: underwent right-sided transfer of the FDS/FCR to the biceps branch of the MCN. The sixth patient is a C6 ASIA A/IC3: underwent supinator to PIN and brachialis to AIN. The seventh patient was a C4 ASIA A/IC0: underwent spinal accessory to FDS/FCR transfer. The eighth patient was a C6 ASIA A/IC3: underwent brachialis to FDS and supinator to PIN transfer. Patient nine C4 ASIA B/IC3: underwent brachialis to FDS/FCR and supinator to PIN transfer. Patient ten C6 ASIA B/IC4: underwent brachialis to AIN/FDS/FCR transfer and supinator to PIN. Patient eleven was a C4 ASIA A/IC0: underwent spinal accessory to middle trunk/triceps transfer. Patient twelve was a C5 ASIA B/IC3: underwent brachialis to FDS/AIN and supinator to PIN. Patient thirteen is a C5 ASIA A/IC1: underwent brachialis to FDS/AIN and supinator to PIN. Patient fourteen is a C5 ASIA A/IC2: underwent brachialis to FDS/AIN and supinator to PIN. Patient fifteen is a C6 ASIA A/IC4: underwent brachialis to FDS/AIN and supinator to PIN. Patient sixteen is a C6 ASIA B/IC3: underwent brachialis to FDS/AIN and supinator to PIN. Patient seventeen is a C6 ASIA A/IC3: underwent brachialis to FDS/AIN and supinator to PIN and recent axillary to triceps. Patient Eighteen is a C6 ASIA A/IC3: underwent brachialis to FDS/AIN and supinator to PIN. Patient Nineteen is a C5 ASIA A IC1: underwent brachialis to FDS/AIN and supinator to PIN. Patient twenty is a C6 ASIA A/IC3: underwent underwent brachialis to FDS/AIN and supinator to PIN.

Major Task 3: Participant recruitment, therapy, participant evaluation

2. Patient one is >36 months out from surgery. He has 4/5 active contraction of his triceps muscle and is 4-/5 in finger extension and 4-/5 finger flexion. Patient two is 36 months out from her surgery. She has 2-3/5 in FPL and FDP function. Patient three is 36 months out from his surgery and has EMG evidence of reinnervation, with 0/5 elbow flexion. Patient 4 is > 36 months out from his surgery and has 3/5 finger flexion. Patient five is > 36 months out from surgery and has 3/5 elbow flexion with 45-60 degrees of flexion. Patient six is > 36 months out from left sided surgery and has 4/5 finger flexion and 2+/5 finger extensors and 32 months out from right sided surgery and has 4/5 finger flexion and 3/5 finger extension. Patient seven is >36 months out from surgery and has 0/5 elbow flexion. Patient eight is >36 months out from surgery and has 4/5 finger extension and 1-2/5 finger flexion. Patient nine is >36 months out but has not been seen for >12 months, at last follow up he had 3/5 finger extension and 1/5 finger flexion. Patient ten is >36 months out and has 3/5 finger extension and 1/5 flinger flexion. Patient eleven is >36 months out from surgery and has 3-4/5 triceps function. Patient twelve is >36 months out from surgery and is due for his 36-month follow-up appointment and has 4/5 finger extension and 3/5 finger flexion. Patients 13 is deceased/withdrawn. Patient 14 is >36 months post-op he has 3/5 EPL function, 1/5 finger flexion and 2+/5 triceps function. Patient 15 is 35 months out from surgery and has 3/5 finger flexion and 4+/5 finger extension. Patient 17 is 33 months post-op and has regained 4/5 finger extensors and 2/5 finger flexors. Patients 18 is 24 months post-op and 2-3/5 finger flexion and 3+/5 finger extension. **Patient 19 is 36 months out from surgery and has recovered per patient report, but due to COVID has not been back to see me in person he is scheduled to see me at the end of November. Patient 20 a is <24 months and is continuing with outpatient hand and physical therapy. He is also scheduled to see me in December 2021 for a physical and clinical assessment.**

Major Task 4: Data Analysis

1. Milestone in progress: Nineteen patients have reached the final 36 -month final follow-up. Patients have continued to make progress up to the 24-month follow-up initially proposed end-point. We expect to publish our final data in a peer-reviewed Neurosurgery or Orthopedic spine journal. This submission should be ready for submission in early 2022.

What opportunities for training and professional development has the project provided?

Nothing to report

How were the results disseminated to communities of interest?

I have given sixteen invited national/international presentations – discussing the ongoing Department of Defense clinical trial and our results up to this point. Since the last annual report, I was an invited speaker for five presentations highlighting both my pre-award work as well as my ongoing efforts supported by the Department of Defense. This has provided me the opportunity to disseminate my work among Neurosurgery, Orthopedic, and PM&R colleagues. Included below of the six presentations since my last annual report. Cumulatively over the course of the award I gave twenty-two national and international presentations.

Jan 2021 - Visiting Professor Grand Rounds – Jefferson University, "Nerve transfers for tetraplegia", Philadelphia, PA
Mar 2021 - Visiting Professor Grand Rounds – Cornell University, "Nerve transfers for tetraplegia", New York, NY
July 2021- ASIA annual meeting "Nerve transfers for tetraplegia", St. Louis, MO
July 2021- CNS/AANS Spine & Peripheral Nerve Section Meeting "Nerve transfers for spinal cord injury – a clinical trial", San Diego, CA
Sept 2021- Keynote Speaker - Austrian Neurosurgical Society "Nerve transfers for tetraplegia" Klagenfurt, Austria
Oct 2021- European Society of Neurological Surgery Peripheral Nerve Section "Nerve transfers for tetraplegia"

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

To date there are nothing to report

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Presentations

1) University of Texas, Houston – Grand Rounds December 2015, Houston, TX – Paradigm shift, nerve transfers to improve upper extremity function following cervical spinal cord injury
2) National Neurotrauma Society Meeting – June 2016, Lexington, KY – Nerve Transfers for Cervical Spinal Cord Injury
3) One Clinic Neurosurgery Course – Keynote speaker August 2016, Springfield, MO - Nerve transfers for spinal cord injury
4) University of Iowa – Annual Research Conference October 2016, Iowa City, IA - Nerve transfers for spinal cord injury
5) University of Utah – Grand Rounds February 2017, Salt Lake City, UT - Nerve transfers for spinal cord injury
6) American Association of Orthopedic Surgeons – Annual meeting March 2017, San Diego, CA - Nerve transfers for spinal cord injury
7) World Federation of Neurosurgery – Peripheral Nerve Course October 2017, Belgrade, Serbia – Innovation in the management of cervical spinal cord injury
8) University of Calgary – Grand Rounds April 2018, Calgary, Canada – Nerve transfers for cervical spinal cord injuries.
9) American Spinal Injury Association – Annual meeting May of 2018, Rochester, MN – Innovation in the management of cervical spinal cord injury
10) World Federation of Neurological Surgeons – Sept 2018, Frankfurt, Germany - Nerve transfers for spinal cord injury
11) World Federation of Neurological Surgeons – Sept 2019, Buenos Aires, Argentina - Where have we been and where are we going, nerve transfers for spinal cord injury
12) Sept 2019 - Academy of Neurological Surgery “Nerve Transfers for tetraplegia”, Rome, Italy
13) Sept 2019 - European Society of Neurological Surgery “Nerve Transfers for cervical spinal cord injury”,
Dublin, Ireland

14) Oct 2019 - Congress of Neurological Surgeons "Nerve Transfers for cervical spinal cord injury", San Francisco, CA
15) May 2020 - Visiting Professor Grand Rounds – Northwestern University "Nerve transfers for tetraplegia", Chicago, IL
16) July 2020 - Norcal Spinal cord injury – featured speaker - "Nerve transfers for tetraplegia", San Francisco, CA
17) Jan 2021 - Visiting Professor Grand Rounds – Jefferson University, "Nerve transfers for tetraplegia", Philadelphia, PA
18) Mar 2021 - Visiting Professor Grand Rounds – Cornell University, "Nerve transfers for tetraplegia", New York, NY
19) July 2021 - ASIA annual meeting "Nerve transfers for tetraplegia", St. Louis, MO
20) July 2021 - CNS/AANS Spine & Peripheral Nerve Section Meeting "Nerve transfers for spinal cord injury – a Clinical trial", San Diego, CA
21) Sept 2021 - Keynote Speaker - Austrian Neurosurgical Society "Nerve transfers for tetraplegia" Klagenfurt, Austria
22) Oct 2021 - European Society of Neurological Surgery Peripheral Nerve Section "Nerve transfers for tetraplegia" Brussels, Belgium

Journal publications.

Dibble CF, Khalifeh JM, VanVoorhis A, Rich JT, **Ray WZ**. Novel nerve transfers for motor and sensory restoration in high cervical spinal. cord injury. *World Neurosurgery*. 2019; Epub

Khalifeh JM, Dibble CF, Voorhis AV, Doering M, Boyer MI, Mahan MA, Wilson TJ, Midha R, Yang L, **Ray WZ**. Nerve Transfers in the Upper Extremity following Cervical Spinal Cord Injury. Part 1: Systematic Review of the Literature. *Journal of Neurosurgery: Spine*. 2019; Epub

Khalifeh JM, Dibble CF, Voorhis AV, Doering M, Boyer MI, Mahan MA, Wilson TJ, Midha R, Yang L, **Ray WZ**. Nerve Transfers in the Upper Extremity following Cervical Spinal Cord Injury. Part 2: Preliminary Results of a Prospective Clinical Trial. *Journal of Neurosurgery: Spine*. 2019; Epub

Dibble CF, Javeed S, Khalifeh JM, Midha R, Yang LJS, Juknis N, **Ray WZ**. Optimizing nerve transfer surgery in tetraplegia: Clinical decision making based on innervation patterns in spinal cord injury. *Journal of Neurosurgery*. 2021; Epub

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

1. Wilson Ray – PI, 15% effort –	Oversees and coordinates all aspects of patient care and recruitment. Performs all surgical interventions.
2. Marty Boyer – CoPI, 5% effort –	Performs independent pre-operative assessments for potential tendon transfers. Assists with patient recruitment/enrollment.
3. Linda Koester – study coordinator 100% effort -	Coordinates pre- and post operative care for all patient Assists with candidate screening and recruitment. Institutional IRB oversight and compliance.
4. Neringa Juknis – Co-Investigator, 10% effort –	Performs independent pre- and post-operative assessments for all outcome measures. Assists with candidate identification and enrollment.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report

What other organizations were involved as partners?

- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: