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TITLE: Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back

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Early management of blood pressure (BP) may be critical to outcome after spinal cord injury (SCI), but evidence-based protocols are needed. Optimal early treatment and management of SCI has not been established in clinical practice, nor in animal models. Guidelines for management of BP in acute SCI have been influenced by the rather clear evidence of a relationship between hypotension and poor outcomes in TBI, and the aim of maintaining cerebral blood flow in the face of increased intracranial pressure (ICP), but doubt remains about what is best for SCI. This grant focuses on the following two hypotheses: 1) Episodes of low BP (measured by mean arterial pressure (MAP) and systolic BP) in the early management of clinical SCI predict worse long-term functional outcomes, and 2) spontaneous hypotensive episodes in the perioperative period of experimental SCI in rats will result in worse outcomes. Both clinical data and experimental modeling studies address these specific hypotheses.
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Progress Report – Year 1
Award Number: W81XWH-13-1-0297
Log Number: SCI20259
Project Title: Effects of Early Acute Care on Autonomic Outcomes in SCI: Bedside to Bench and Back
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Accomplishments
1. UCSF Animal Protocol and ACURO Protocol approvals were received.
2. Human Subjects Protocol approval letters were received from SFGH, Santa Clara Valley Medical Center and Palo Alto VA Health Sciences Center have been forwarded to the DoD and were approved.
3. Established surgical methods for implanting Data Sciences refurbished blood pressure transducers in rats and conducted preliminary experiments to assess the surgical procedure outcomes and the consistency of the blood pressure data in rats. We have also updated the data collection methods for the animal studies.
4. Tested effect of 200 kilodyne impact at T2-3, on recovery of locomotor function in a group of pilot rats used for evaluating the agents to control BP over 4 hours post SCI.
5. Initiated an analysis of drug delivery techniques using phenylephrine, dopamine, and norepinephrine to determine infusion rate, method of delivery, concentration, etc. for holding blood pressure at specified levels for 4 hours after SCI.
6. Held meetings with SFGH clinicians to identify methods for, and people who will participate in collecting data from SFGH patient records for the retrospective and prospective study. For the retrospective study, we were able to access the large existing database containing q 1min blood pressure data from SFGH SCI patients from 2007-2013. CHR approval was extended to 2013 for retrospective analysis.
7. Held meetings with Drs. Creasey and McKenna to identify procedures for accessing data from Santa Clara Valley Medical Center and Palo Alto VA Health Sciences Center.

Major Task 1: Regulatory set up for animal and human studies (Specific aims 1-3)
Subtask 1: UCSF Retrospective study IRB approval
A submission to modify a current IRB approval for retrospective chart review for this project has been submitted and approved.

Subtask 2: UCSF IACUC approval
The UCSF IACUC approval was obtained and then submitted to ACURO and approval was received Jan. 15, 2014.

Subtask 3: PAVAHCS and SCVMC retrospective study IRB approvals
The VA approval and the SCVMC approval have been completed, the subcontracts for these organizations have been finalized, and the IRB information submitted the the DoD for approval.

Specific Aim 1: Examine the available evidence for a correlation between early BP (and bladder/bowel) management, vasopressor use, and later outcomes, including outcomes on autonomic, bladder and bowel function. (year 1-2)

Major Task 2:
Retrospective review of paper and electronic medical records of SCI patients
We have held meetings with the SFGH spinal cord injury clinicians and have established methods for accessing a large dataset collected over the past several years from the ICU using the Aristein monitoring system which contains q 1min blood pressure data for all SCI patients during their ICU stay. Data have been loaded into the HIPA compliant database ‘RedCap’ for querying. Dr. Whetstone has already organized other data from most of these SCI patients treated at SFGH; this data has been matched to the data in the Aristein monitoring system by Dr. Gregory Hawryluk who was able to access the BP data using Matlab programs that he wrote. We have analyzed the q 1 min data on physiological monitoring of all SCI patients seen between 2005 and 2011 and compared it to the ASIA grade status over the ICU stay. The data show that patients with more epochs of low BP show worsening AIS motor scores (from Hawlyruk et al., 2014, submitted). We presented this first analysis at the National Neurotrauma Society meetings in San Francisco on June 30, 2014. The advantage of these data is that it doesn’t only show average MAPs but shows every instance of low blood pressure during the entire recording period from admission to discharge in the ICU. There was a significant relationship between the number of epochs of MAP below 80 and poorer outcome at discharge from the ICU providing initial support for the hypothesis driving this grant. This paper has been submitted to the Journal of Neurotrauma for publication and is appended at the end of this file.
Specific Aim 2: Provide detailed reports and physiological monitoring in the pre-hospital, ED and ICU to identify cardiovascular parameters and (events) during early management of SCI that are associated with poor outcome, including bowel and bladder function.

Major Task 4: Perform detailed physiological monitoring in the ED and ICU for 1st 7 days after SCI.

Subtask 1: Use prior SCI+TBI and early results of consortium BP record evaluations to finalize data collection strategy for prospective study. We have currently set up a RedCap database and are finalizing the data entry forms for the prospective study based on our retrospective analyses.

Subtask 2: Train and coordinate investigators and clinical staff in ED, ICU, and rehab. New members have been added to the SFGH/UCSF group to participate as clinical investigators including Sanjay Dhall, MD, Neurosurgery, Jason Talbott MD, PhD Radiology, Jonathan Pan MD, PhD, Anesthesiology, will join co-investigators William Whetstone MD from Emergency Medicine and Geoffrey Manley MD, PhD who are already on the project. This team will also be conducting a related but separate prospective study entitled “Canadian Multicentre CSF Monitoring and Biomarker Study” CAMPER. The Rick Hansen Institute has agreed to send trainers to train and certify our clinical coordinators and nurse-practitioners to perform ASIA sensory and motor scoring. We will be sharing clinical coordinators with the large prospective observational study TRACK-TBI which will allow us, with limited funds, to cover 24/7 enrollment of SCI patients. The human subjects protocols are being submitted to our IRB.

Specific Aim 3: Determine the effects of episodes of hypotension and hypertension on the recovery of locomotor and bladder and bowel function in our rat model of high thoracic contusion SCI. We will examine the effects of commonly used vasopressors on outcome.

Major Task 5: Establish methods for BP regulation using the proposed hypo- and hypertensive treatments in the high thoracic injury model.

Subtask 1: Consult with clinical investigators to appropriately model the cardiovascular manipulations in the animal study.

We have enlisted the participation of Dr. Jonathan Pan MD, PhD of the Anesthesia Department who has training in SCI research, to help with this aspect of the project.

Subtask 2. Perform control study in rats with high thoracic SCI to determine appropriate drug and dosing for hypo- and hypertensive treatments. (see below)

Major Task 6: Perform high thoracic, moderate-severe SCI in cohorts of rats and monitor BP, bladder and bowel functional measures, and locomotor function over 6 weeks. Groups will include a) control group - no manipulation or treatments; b) group with MAP maintained at 75 with dopamine; c) group with BP maintained at 90 mm Hg using pressors; d) hypertensive group – BP maintained at 120 mm Hg induced with pressors.

Subtask 1: Implant telemetric pressure transducers for continuous monitoring of BP and activity in rats.
**Subtask 2:** Induce high thoracic injuries and monitor recovery of BP, bladder/bowel function, locomotor function.

We have tested the effect of a 200 kilodyne impact using the Infinite Horizons contusion device at T2-3, on recovery of locomotor function in a group of pilot rats. This level of injury reliably produced an initial severe deficit followed by a fairly rapid recovery of weight supported stepping; but, the animals never recovered consistent forelimb-hindlimb coordination over the 6 weeks post-injury survival time (mean BBB final score of 12). Spontaneous urination was observed at a mean of 4.2 days. Thus, we will be able to detect both deleterious as well as improvements in function as a result of the early post-injury manipulation of blood pressure (BP).

We continued working to establish the surgical and procedural methods for continuous telemetric monitoring of blood pressure in the rats after spinal cord injury at the high thoracic level using the chronically implanted Data Science transducers. After piloting the surgical procedures for implanting the transducers and testing the data collection system, we proceeded to implant transducers in a group of 6 animals with SCI and blood pressure, bladder function and locomotor recovery was monitored up to 6 weeks. Immediately post-SCI, we collected data from 3 injured control animals to establish baseline BP and to determine the effects of the anesthesia (2% isofluorane) used during the 4 hour post-injury BP manipulation period; these animals were followed for 6 weeks with BP monitoring, bladder function and behavioral testing. In another set of animals, we began to work out the pharmacologic methods for setting blood pressure. We used phenylephrine, norepinephrine and dopamine in different animals. While we were able to manipulate the BP, it was not consistent and we determined that regardless of the agent, the tail vein approach we were using was not optimal. Adequate infusion rates were difficult to produce.

Ideally, we would like to manipulate the blood pressure quickly and effectively to the desired MAP. In the first cohort, the turn around time was about an hour and was ineffective. We focused on improving several things including:

1) Drug delivery. There were some doubts that the tail vein was an effective route to immediately deliver and impact blood pressure systemically. There were some issues with the tail stiffening from possible vessel damage and leakage into the surrounding tissue. We thought that perhaps the femoral vein would be better as it is larger. So in one subject, we catheterized the femoral for comparison to ensure that the pressors were in fact effectively metabolized systemically at the same rate as via the tail vein. We then went back to the tail vein and tried a new approach to catheterizing the tail vein using a stylet and smaller diameter catheter. After obtaining continuous blood flow (1-2 drops) with the needle pre-threaded with a stylet, the stylet was advanced a maximum of 1 cm into the tail. Keeping the stylet in place, the needle was removed and replaced with the catheter. Once the catheter reached the tail entry point, both the catheter and stylet were inserted together 2 cm into the tail, for a total maximum of 3 cm into the tail vein. The stylet was removed and the vein preserved, minimizing vessel damage and proximal leakage,
for reliable drug delivery for four hours. In all rats with modified tail vein catheter placement (now n=3), we were able to titrate drug infusion and reach target MAP within 5-10 minutes after spinal cord impact.

Due to additional symptoms (i.e. excessive drooling and bulging eyes) associated with the infusion of these vasoactive drugs, the starting concentrations of drugs were lowered, which are more clinically relevant. Isoflurane concentration also was maintained at about 1.5% and possibly also helped to relieve these symptoms. For more effect, the rate of infusion was increased, however a maximum ceiling occurred even at higher infusion rates and concentrations. At this point, we think that norepinephrine may be the best drug to manipulate blood pressure. Infusion with norepinephrine (0.2 mg/ml) at 3.0-5.6 ul/min maintained a mean arterial pressure between 115 and 130 (n=2). Dopamine (0.08 mg/ml) administration at 50-70 ul/min produced a mean arterial pressure between 82 and 115 and over the 4 hours, more dopamine would not increase the animal’s MAP, reaching a ceiling of 89 (n=1).

**Cardiovascular maintenance immediately post-SCI for 4hrs**

![Graph showing MAP over time with different drug infusions.]
We were also having some complications with the transducer readings. In two animals, systolic readings on the telemetry device were not reliable because the systolic waveforms were dampened on the graph, most likely due to catheter tip occlusion post-op by a blood clot. Blood clots in the arterial catheter are likely interfering with the transducer. Although it wouldn’t affect the mean arterial pressure (MAP), pulse pressures (difference between systolic and diastolic pressure) were significantly reduced. We may try dipping catheter tip in heparin saline solution prior to implanting to minimize blood clotting. We will implement this change in future transducer placement.
We are still establishing the BP manipulation protocols but are nearly there, and anticipate that we will begin the study in earnest in the next couple of months.

Subcontract sites report:
Prepared by Dr. Stephen McKenna (Santa Clara Valley Medical Center) and Dr. Graham Creasey (Palo Alto VA Health Sciences Center)

Major Task 1: Regulatory set up for animal and human studies (Specific aims 1-3)
Subtask 3: PAVAHCS and SCVMC retrospective study IRB approvals
Protocol has been approved by the Stanford IRB.
Protocol has been approved by the SCVMC IRB.
Specific Aim 1: Examine the available evidence for a correlation between early BP (and bladder/bowel) management, vasopressor use, and later outcomes, including outcomes on autonomic, bladder and bowel function. (year 1-2)
A literature review has been conducted and an expert community of practice has been interviewed to examine the available evidence for a correlation between early BP (and bladder/bowel) management, vasopressor use, and later outcomes, including outcomes on autonomic, bladder and bowel function. There is very little information about a correlation between early management and later outcomes for autonomic, bladder and bowel function.

Major Task 2: Retrospective review of paper and electronic medical records of SCI patients
A review of paper and electronic charts has been conducted to evaluate the structure and relevance of autonomic system function reporting after spinal cord injury. Medical and urodynamic records of patients in the SCI Units are available on paper for up to 40 years and in electronic form for up to 15 years. The majority of records are in the form of unstructured text although laboratory investigations are available in structured form. Urodynamic records are available in graphical form on paper and in electronic form and are available in exportable electronic format for the last 6 years in the VA SCI Unit.
Subtask 1: Develop SCI Consortium (SCIC) data dictionary and coding manual to include the following (joint meetings of the consortium will be held beginning in Sept, 2013):
• Conformance with NINDS SCI CDEs
• Additional locally defined elements pertinent to the SCIC project aims
• Rules and error flags for data field ranges, relational consistency and completeness
• Measures to safeguard research subject confidential information through elimination of any identifying PHI.
In order to develop the SCIC data dictionary and coding manual, the following four major activities have been undertaken:
1. Bi-weekly TrackSCI team meetings; see attached minutes
i. The TrackSCI team met bi-weekly via Webex teleconferences to direct project efforts. A comprehensive list of meeting days and agendas has been included.

2. Form Review at VA and SCVMC
   i. EPIC admission order sets for the following SCVMC services were reviewed
      SCVMC Trauma, SCVMC Neurosurgery, SCVMC Rehabilitation ICU, SCVMC Spinal Cord Injury Service, SCVMC Traumatic Brain Injury Service
   ii. VA Computerized Patient Record System (CPRS) order sets for admissions and management in the VA SCI Service were reviewed
   iii. Forms for the collection and reporting of autonomic standards were reviewed with clinical staff. There were no consistent forms being used to document autonomic outcomes. This informed our future directions for the partnership.

3. International Standards in EPIC
   i. International effort led by Fin Biering-Sorensen, Past President of the International Spinal Cord Injury Society, has been started to incorporate SCI International Common Data Sets into the Epic Foundation System
   ii. The Canadian (Rick Hansen Institute) algorithm for classification of SCI based on International Standards for Neurological Classification of Spinal Cord Injury is being proposed for incorporation into EPIC
   iii. The TrackSCI team has initiated outreach to participate in the implementation of Autonomic Standards in EPIC

4. Canadian Multicentre CSF Monitoring and Biomarker Study (CAMPER)
   i. Existing goals
      1. Measure the pressure in the spinal fluid surrounding the spinal cord to find out how well the spinal cord is being supplied with blood.
      2. Determine how drugs called "vasopressors", which are used to control blood pressure following SCI (spinal cord injury), influence spinal fluid pressure.
      3. Characterize the severity of an SCI using the levels of specific proteins found within the spinal fluid.
4. Predict how much neurologic recovery may be regained using the levels of specific proteins within the spinal fluid.
5. Identify proteins within the spinal fluid that will help us learn more about what is happening after SCI and assist us in developing new treatments for SCI.

ii. On Sept 29th, 2014, the Rick Hansen Institute / TrackSCI Team conducted a WebEx webinar to demonstrate the RHI Global Research Platform for data collection after SCI.

Subtask 2: Design the SCIC database and electronic Case Report Forms (eCRFs) on a shared platform for SFGH, SCVMC and VAPAHCS and training of data collectors at all 3 sites on abstraction of retrospective data.
Based on the efforts listed in Subtask 1 above, the SCIC database and eCRFs are in the process of development. Two specific types of autonomic data collection dictionaries have been proposed during bi-weekly team meetings: a “minimal” data set based on the ISCoS International Standards to document remaining Autonomic Function after Spinal Cord Injury (ISAFSCI), versus a “maximal” NINDS CDE data dictionary including the Basic Lower Urinary Tract Function, Basic Urodynamic, Extended Bowel Function, Basic Female and Male Sexual Function, Basic Cardiovascular Function, and Basic Skin and Thermoregulation Data Sets. Neither solution was appropriate for prospective data collection, so a hybrid data dictionary is current in development.

Subtask 3: Mapping and migration of existing retroactive patient data sets from SCVMC and SFGH to SCIC database.
Mapping and migration of retroactive patient data depends on finalization of case reporting forms currently under development.

In conjunction with the SCVMC EPIC electronic medical record IT team and a data analyst familiar with the VA CPRS electronic medical record, tools for retrospective data collection are in development. Analysis of urological records for SCI patients in national VA databases for 2002-2012 has been commenced.

Major Task 3: Analyze records of early management (BP and bladder/bowel management including urodynamics), and conduct automated text mining of electronic medical records and medication administration. Identify potential outcomes that do not conform and that may be emerging CDEs.
Digital records of early BP management in the ICU at SFGH have been correlated with outcomes of neurological level and completeness of spinal cord injury. (See UCSF report above).

The format of other records of early blood pressure, bowel and bladder function, and urodynamics have been analyzed in preparation for text mining of
medical records. Records do not conform to existing autonomic standards. Domestic and international leaders in the field of Common Data Element reporting have collaborated to improve recording of autonomic data in patients with spinal cord injury; please see Major Task 2, Subtask 1, items 2 and 3 (above).

**Subtask 1: Data curation and exploratory statistical analysis plan.** Develop data collection forms in HIPAA-compliant UCSF RedCap system to create a secure, queriable data repository. Use bundled de-identification tools and descriptive analytics to clean data. Once de-identified, deploy big-data analytics, including multivariate pattern detectors (e.g., non-linear PCA) and text analysis to describe covariance and text patterns reflecting coherent autonomic changes within the retrospective clinical data record. The goal of this analysis is to fundamentally describe the potential relationship among physiology and autonomic outcomes.

Contingent upon development of text mining strategy, see Major Task 3 (above).

**Subtask 2: Multivariate hypothesis testing.** Harness the results of exploratory analysis in subtask 1 to develop candidate multivariate models to evaluate the predictive capacity of multivariate physiological patterns to predict multivariate outcome patterns. The goal of this analysis is to make decisions about the most important variables to collect in the prospective study in Specific Aim 2.

**Subtask 3:** Continue gathering retrospective data and evaluate for an initial publication describing the consortia collective evidence on BP management and outcomes.

**Specific Aim 2:** Provide detailed reports and physiological monitoring in the pre-hospital, ED and ICU to identify cardiovascular parameters and (events) during early management of SCI that are associated with poor outcome, including bowel and bladder function.

**Major Task 4: Perform detailed physiological monitoring in the ED and ICU for 1st 7 days after SCI.**

**Subtask 1:** Use prior SCI+TBI and early results of consortium BP record evaluations to finalize data collection strategy for prospective study.

Data on veterans with concurrent TBI and traumatic SCI occurring from 1952 to 2012 and undergoing lifetime follow-up in the SCI Unit of the VA Palo Alto has been abstracted from unstructured text in the VA Computerized Patient Record System to test a data collection strategy and to determine the information available, and is being prepared for publication.

**Specific Aim 3:** Determine the effects of episodes of hypotension and hypertension on the recovery of locomotor and bladder and bowel function in our rat model of high thoracic contusion SCI. We will examine the effects of commonly used vasopressors on outcome.

**Major Task 5: Establish methods for BP regulation using the proposed hypotensive and hypertensive treatments in the high thoracic injury model.**
See UCSF report above.

**Major Task 6:** Perform high thoracic, moderate-severe SCI in cohorts of rats and monitor BP, bladder and bowel functional measures, and locomotor function over 6 weeks. Groups will include a) control group - no manipulation or treatments; b) group with MAP maintained at 75 with dopamine; c) group with BP maintained at 90 mm Hg using pressors; d) hypertensive group – BP maintained at 120 mm Hg induced with pressors.

See UCSF report above.

**Subtask 5:** Identify rat CDEs that parallel the human outcomes.

**Final Milestone:** Develop recommendations for early management based on the parallel study of both animal and human outcomes after SCI.