

Prospective study of Mean Arterial Blood Pressure Augmentation in the Treatment of Spinal Cord Injuries (MAP study):

An EAST Multicenter Trial Proposal

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Background significance

The pathophysiology of spinal cord injuries involves both mechanical forces (compression, distraction and transection) and nutrient delivery systems (blood flow, oxygenation).[1,2] A critical aspect of spinal cord recovery is maintaining adequate blood flow to the injured neural tissue.[1,2] Augmentation of blood pressure with elevation of mean arterial pressure (MAP) is part of the modern treatment for traumatic spinal cord injuries (SCI).[1, 3-7] Loss of blood flow autoregulation within the injured spinal cord creates an environment for continued ischemia that can be seen with laser speckle contrast imagery.[8] Elevated MAP goals (>85 mmHg) for four to seven days post injury correlate with improved neurological outcomes, measured by American Spinal Injury Association (ASIA) scores.[1, 3-7] Spinal cord hyperperfusion protocols (Appendix A) appear to be an essential part of early spinal cord injury treatment showing improved neurological outcomes.[1, 3-7]

Spinal cord hyperperfusion protocols start with fluid resuscitation and vasopressor support (Appendix A). The Consortium for Spinal Cord Medicine recommends the use of vasopressors dopamine, norepinephrine or phenylephrine based on injury location.[5,7] Initiation of therapies in injured patients does not appear to be without risk. Complications of vasopressor use are more common in elderly trauma patients and are typified by arrhythmias and elevated cardiac enzymes.[9-12] Along with treatment risks, other details regarding treatment timing, duration and need to achieve set MAP goals during the entire 72-96 hours are lacking in the current literature.

Optimal hyperperfusion care during early spinal cord injury therapy is MAP > 85 mmHg 100% of the treatment protocol (72-96 hours). Even when patients are cared for in intensive care units at level one trauma centers, these goals occur only 75% of the time.[1,13] Hyperperfusion goals are even less likely to occur in patients requiring operative fixation, with one recent study showing 100% of SCI patients had a MAP < 85 during operative interventions.[14]

Approximately 80% of all SCIs occur concurrently with polytrauma, creating tenuous resuscitative circumstances in the setting of multiple potential sources of shock.[15-17] Traumatic SCI treatment typically includes early operative intervention (within first 24 hours post injury) to increase the odds of neurological improvement.[2] Previous studies have demonstrated that the desire for both spinal cord hyperperfusion and early spine fixation creates competing treatment priorities.[14] It has also been shown that transferred trauma patients also have unique unknown treatment specifics as the time difference between time of injury and blood pressure augmentation protocols can vary widely. Specifically cited from a 40 patient case series, community/transferring hospitals had 50% of MAP recordings less than 80mmHg and 20% of MAP recordings less than 80mmHg during transport (18). The interplay between

hyperperfusion timing, spine fixation and complications associated with hyperperfusion therapies during early SCI treatment are yet to be delineated. We feel this is largely due to the lack of large prospective data registries specifically designed to investigate this population and the investigative questions to follow.

Specific aims:

Primary aim:

1. Determine the amount of time (hours) patients on MAP protocol reach the goal of a MAP >85mmHg.
2. Determine the proportion of SCI patients that meet a MAP goal of >85mmHg for 90% of their treatment duration.

Secondary aims:

1. Compare the MAP outcomes (time patients have MAP < 85mmHg and proportion of time MAP goal < 85mmH) between trauma transfers and direct from scene patients.
2. Determine the cardiogenic complications (atrial fibrillation, ventricular arrhythmia and troponin elevation) of patients on MAP treatment with vasopressor medications.
3. Determine how polytrauma (based on ISS scores) influences MAP treatment.

Experimental design

1. Inclusion criteria:
 - Blunt trauma patients with spinal cord injury on MAP protocol
 - Age > 18
 - Admission date 10/1/2021-10/1/2022
2. Exclusion criteria:
 - Patients under the age of 18
 - Non trauma patients undergoing surgical decompression and/or stabilization on MAP protocol
 - Incomplete neurological exam documented on hospital admission
 - Pregnant
 - Prisoners
 - Penetrating trauma
3. Therapeutic interventions
 - a. Prospective observation study. Patients will be managed according to the standards of the treating physicians or institutional protocols.

Outcomes

Primary:

1. Neurologic improvement (specifically change in ASIA score) from admission to post-map protocol and at discharge in those patients who met a MAP goal for greater

than 75% of their first 24 hours of treatment.

Secondary:

1. Determine the complications of vasopressor use in maintenance of elevated MAP goals.
2. Determine the influence pre-receiving hospital transfer treatment and time effects on the overall course of SCI patients in regard to neurological outcomes.
3. Determine the patient specific, injury specific and treatment specific influences on neurologic improvement in SCI patients.

Variable list

Demographics, injury and hospitalization variables, operative-specific variables, neurological exam values, MAP data, vasopressor data, daily laboratory and vital signs, complications, and invasive procedure data will be collected for patients included in this study. MAP values will be recorded on an hourly basis with time 0 representing the first MAP value recorded post-injury. Each subsequent hour will be recorded, any missing hours will be noted in the data collection tool.

These data points are collected as standard of care for patients treated for traumatic SCI at most trauma centers. Only the designated study staff will have access to the REDCap database created solely for use in this study.

Data collection and Statistics

Multi-institution study including level 1 and level 2 trauma centers. This will be a prospective review of retrospectively collected data to identify all trauma patients being treated with hyperperfusion protocols for spinal cord injury at their respective institution. Patients will be identified from the trauma registry at each institution. A review of the institutions electronic medical record system will be utilized to calculate the neurological exam score. The investigators will also utilize their respective trauma registries and electronic medical record system to obtain the complete list of study variables.

Simple comparisons of continuous variables between independent groups (neurologic improvement vs no improvement) will be made using two-sided, two-sample t-tests. For ordinal variables, simple comparisons will use Wilcoxon two-sample tests. Categorical or dichotomous variables will be compared between independent groups using chi-square tests. Models that control for relevant covariates will be based on logistic regression for dichotomous outcomes and analysis of covariance (ANCOVA) for continuous outcomes. When sample estimates (e.g. average fraction of time MAP <85) are presented, 95% confidence intervals will be constructed around each point estimate. Intraoperative MAP values will be analyzed similarly to non-operative MAP values as above. Descriptive statistics will be reported as mean +/- standard deviation for continuous variables, and as frequencies with percentages for categorical or dichotomous variables. Logistic regression was used to model neurological improvement (as a dichotomous outcome) as a function of a set of potential predictors.

Area under curve (AUC) calculation will be performed for each patient as a function of time spent below a MAP of 85 mmHg. Where $a_1:b_1$ are the first time points where the patients MAP value crosses below MAP of 85 mmHg. $f(x)$ represents a single patients MAP pressure curve for 96 hours of the hyperperfusion therapy.

$$AUC = \int_{a_1}^{b_1} f(x) dx + \int_{a_2}^{b_2} f(x) dx + \dots \int_{a_x}^{b_x} f(x) dx$$

Power analysis:

Gaudin et al (J Neurosurg Spine 32:127-132, 2020) found that episodes of relative intraoperative hypotension ($MAP \leq 85$ mm Hg) occurred 51.9% of the total OR time in their study. If our retrospective study were to find that result, our sample of $n= 200$ patients would provide an estimate precision (i.e. 95% confidence interval) of (45.0%, 58.8%).

Consent procedures

This is a prospective observational study in which patients are managed according to the discretion of the institution, so a waiver of consent is requested. With transfer of data to the REDcap form there will be no patient identifiers.

Risk Benefit analysis

Given the observational nature of the study, the only potential risk associated with this study is loss of confidentiality, which will be minimized by limiting access to data and de-identifying data within the REDcap data collection tool. The information from this study will be used to help to improve care by providing a clearer understanding of how early hyperperfusion therapy correlates with neurologic outcomes in patients with spinal cord injuries.

References

1. Hawryluk G, Whetstone W, Saigal R, Ferguson A, Talbott J, Bresnahan J, Dhall S, Pan J, Talbott J, Manley G. Mean arterial blood pressure correlates with neurological recovery after human spinal cord injury: Analysis of high frequency physiological data. J Neurotrauma. 2015;32(5):1958-67.
2. Fehlings MG, Vaccaro A, Wilson JR, Singh A, Cadotte DW, Harrop JS, Aarabi B, Shaffrey C, Dvorak M, Fisher C, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One. 2012;7(2):e32037.

3. Levi L, Wolf A, Belzberg H. Hemodynamic parameters in patients with acute cervical cord trauma: a descriptive, intervention and prediction of outcome. *Neurosurgery*. 1993;33:1007-17.
4. Walters BC, Hadley MN, Hurlbert RJ, Arabi B, Dhall SS, Gelb DE, Harrigan MR, Rozelle CJ, Ryken TC, Theodore N. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 Update. *Neurosurgery*. 2013;60:82-91.
5. Wing, PC. Early acute management in adults with spinal cord injury: A clinical practice guideline for health-care professionals. Who should read it? *J Spinal Cord Medicine*. 2008;31:403-79.
6. Saadeh YS, Smith BW, Joseph JR, Jaffer SY, Buckingham MJ, Oppenlander ME, Szerlip NJ, Park P. The impact of blood pressure management after spinal cord injury: a systematic review of the literature. *J Neurosurgery*. 2017;43(5); 1-7.
7. Vale FL, Burns J, Jackson AB, Hadley MN. Combined medical and surgical treatment after acute spinal cord injury: results of prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. *J Neurosurgery*. 1997;87;239-46.
8. Gallagher MJ, Hogg FRA, Zoumprouli A, Papadopoulos MC, Saadoun S. Spinal cord blood flow in patients with acute spinal cord injuries. *J Neurotrauma*. 2019;36(6);919-29.
9. Readdy WJ, Whetstone WD, Ferguson AR, Talbott JF, Inoue T, Saigal R, Bresnahan JC, Beattie MS, Pan JZ, Manley GT, et al. Complications and outcomes of vasopressor usage in acute traumatic central cord syndrome. *J Neurosurgery*. 2015;23(5);574-80.
10. Readdy WJ, Saigal R, Whetstone WD, Medfford AN, Ferguson AR, Talbott JF, Inoue T, Bresnahan JC, Beattie MS, Pan J, et al. Failure of mean arterial pressure goals to improve outcomes following penetrating spinal cord injuries. *Neurosurgery*. 2016;79(5);708-14.
11. Inoue T, Manley GT, Patel N, Whetstone WD. Medical and surgical management after spinal cord injury: Vasopressor usage, early surgeries, and complications. *J Neurotrauma*. 2014;31(3);284-91.
12. Yue JK, Tsolinas RE, Burke JF, Deng H, Upadhyayula PS, Robinson CK, Lee YM, Chan AK, Winkler EA, Dhall SS. Vasopressor support in managing acute spinal cord injury: current knowledge. *J Neurological Sciences*. 2017;63(3);308-17.
13. Kong CY, Hosseini AM, Belanger LM, Ronco JJ, Paquette SJ, Boyd MC, Dea N, Street J, Fisher CG, Dvorak MF, et al. A prospective evaluation of hemodynamic management in acute spinal cord injury patients. *Spinal cord*. 2015;51;466-71.
14. Gaudin XR, Wochna JC, Wolff TW, Pugh SM, Pandya UB, Spalding MS, Narayan, KK. Incidence of intraoperative hypotension in acute traumatic spinal cord injury and associated factors. *J Neurosurgery*. 2019;32(1);127-32.

15. Yue JK, Winkler EA, Rick JW, Deng H, Partow CP, Upadhyayula PS, Birk HS, Chan AK, Dhall SS. Update on critical care for acute spinal cord injury in the setting of polytrauma. *J Neurosurgery*. 2017;43(5):E19.
16. Burney RE, Maio RF, Maynard F, Karunas R. Incidence, characteristics, and outcome of spinal cord injury at trauma centers in North America. *Arch Surg*. 1993;128(5):596-599
17. Catapano JS, John Hawryluk GW, Whetstone W, Saigal R, Ferguson A, Talbott J, Bresnahan J, Dhall S, Pan J, Beattie M, Manley G. Higher Mean Arterial Pressure Values Correlate with Neurologic Improvement in Patients with Initially Complete Spinal Cord Injuries. *World Neurosurgery*. 2016;96:72-79.
18. Tee JW, Altaf F, Belanger L, Ailon T, Street J, Paquette S, Boyd M, Fisher CG, Dvorak MF, Kwon BK. Mean arterial blood pressure management of acute traumatic spinal cord injured patients during the pre-hospital and early admission period. *J Neurotrauma*. 2017;34:1271-1277