The Impact of Mean Arterial Pressure on Functional Outcome Post-Acute Spinal Cord Injury: A Systematic Review of Animal Models and Human Clinical Data

By

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Abstract:

The occurrence of hypotension has been shown to be associated with worse outcomes after traumatic injury, including severe head injury. To our knowledge, a prospective controlled assessment of the effects of hypotension on acute spinal cord injury (ASCI) in humans has not been performed. Animal models of ASCI have been created in laboratory and data is extrapolated to the clinical setting, suggesting that hypotension contributes to secondary injury after ASCI by reducing spinal cord blood flow and perfusion. Current AANS guidelines claim that there is insufficient evidence to support treatment guidelines. The "options" given include maintaining a MAP of 85-90 for first 7 days following ASCI "to improve spinal cord perfusion". These recommendations are supported by Class III evidence only; strong scientific evidence is lacking with respect to the actual target MAP that should be achieved in ASCI patients with respect to the actual target MAP and length of time for target MAP post injury. Given the lack of conclusive evidence on the topic, we set out to perform a comprehensive review of the pertinent evidence, first of the animal models on which the current guidelines are based, followed by a review of the human clinical data which is available. The goal was to assess the merit of the current guidelines and ascertain the correct target MAP immediately after ASCI as well as the duration for which this MAP must be targeted. Based on the data collected, we then designed a prospective pilot study to be able to address the question of the effect of MAP and its duration on the functional outcome in ASCI patients.

Methods:

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers was conducted for both animal models as well as human clinical data. The data is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Summary tables were then created for each set of data.

Results:

Our search strategies yielded 2925 animal model papers and 3130 human papers. After manual de-duplication and application of inclusion/exclusion criteria to the abstracts obtained, we were left with 13 relevant animal studies and 49 human studies. After manually searching through the reference sections of all of the titles of interest obtained, 42 studies were added to the animal studies and 18 studies were added to the human studies, bringing our totals to 55 animal and 67 human papers respectively. After applying our strict inclusion/exclusion criteria to the full texts obtained, we were left with 10 animal and 9 human studies. These studies were then analyzed and summarized into three tables. Due to the heterogeneity of the data a meta-analysis was not performed.

Conclusions:

Although the data collected did not allow us to come to a definitive conclusion regarding the worth of the current AANS guidelines regarding MAP directed therapy in ASCI patients, it is an invaluable summary of the all of the positive and negative data available in both animal models and human clinical data. It allowed us an overview of the pitfalls and limitations of previous studies as well

as an index of the gaps that required filling in order to come to a definitive conclusion. The data collected permitted us to design a focused prospective pilot study addressing targeted MAP goals and duration in the ASCI patient population.

Acknowledgements:

I would like to acknowledge Professor Anthony Kaufmann for encouraging me to complete a masters degree and Professor Neil Berrington for making it happen. A special thanks to Professor Brian Schmidt and Professor Sadeesh Srinathan for their invaluable contributions to this text.

Dedication:

This thesis and degree are dedicated to everyone who ever doubted me. Thank you for giving me the strength to carry on. In the end, it is truly our defiance that redeems us.

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General Introduction:

Traumatic spinal cord injury is a common but devastating injury that affects approximately 4300 Canadians every year (1), costing the health care system 2.7 billion dollars (2). Since the advent of modern medicine, the potential for recovery of a complete spinal cord injury has been considered poor; there is a cornucopia of research addressing spinal cord regeneration as well prevention of secondary injury of the spinal cord after a primary insult. The occurrence of hypotension has been shown to be associated with worse outcomes after all traumatic injury, including severe head injury. To our knowledge, a prospective controlled assessment of the effects of hypotension on acute spinal cord injury (ASCI) in humans has not been performed. Animal models of ASCI have been created in laboratory and data is extrapolated to the clinical setting, suggesting that hypotension contributes to secondary injury after ASCI by reducing spinal cord blood flow and perfusion. Current AANS guidelines (3) claim that there is insufficient evidence to support treatment guidelines. The "options" given include maintaining a MAP of 85-90 for first 7 days following ASCI "to improve spinal cord perfusion". These recommendations are supported by Class III evidence only; strong scientific evidence is lacking with respect to the actual target MAP that should be achieved in ASCI patients with respect to the actual target MAP and length of time for target MAP post injury. Given the lack of conclusive evidence on the topic, we set out to perform a comprehensive review of the pertinent evidence, first of the animal models on which the current guidelines are based, followed by a review of the

human clinical data which is available. The goal was to assess the merit of the current guidelines and ascertain the correct target MAP immediately after ASCI as well as the duration for which this MAP must be targeted. Based on the data collected, we then designed a prospective pilot study to be able to address the question of the effect of MAP and its duration on the functional outcome in ASCI patients.

The animal models and human clinical data were analyzed separately and written up as two distinct papers, which were submitted for publication. These two papers form the crux of this thesis, as well as the basis for the design of the pilot study.

Bibliography:

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Chapter I

Animal Studies

The Impact of Mean Arterial Pressure on Functional Outcome Post-Acute Spinal Cord Injury: A Systematic Review of Animal Models

Introduction:

The management of acute spinal cord injury (ASCI) has long been a controversial topic. Experimental evidence suggests that after the initial episode of cord injury and compression, there is an active secondary phase of injury (1,2). Secondary injury mechanisms include vascular changes such as reduction in blood flow, loss of autoregulation, neurogenic shock, hemorrhage, loss of microcirculation, vasospasm and thrombosis. Other secondary injury mechanisms include biochemical changes leading to necrosis, electrolyte shifts, edema and loss of energy metabolism. There is some experimental evidence to suggest that there might be a critical period immediately after injury when some of the secondary mechanisms of injury may be countered (3,4,5).

In order to counter the decrease blood flow produced by ASCI, it is a currently employed therapy to increase the blood pressure immediately post injury. There is some evidence to suggest that an increase in blood pressure leads to significant improvement in axonal function both in the motor and somatosensory tracts of the cord (8). The evidence, however, is insufficient to definitively recommend universally increasing the MAPs in patients presenting with ASCI. Only Class III evidence exists that mean arterial pressure (MAP) directed therapy, goal 85 to 90 mm Hg, in patients with ASCI improves neurological outcome. Strong scientific evidence is lacking with respect to the actual target MAP that should be achieved in ASCI patients as well as the length of time the MAP should be targeted post injury. Current AANS guidelines (18) claim that there is insufficient evidence to support

treatment guidelines. The "options" given include maintaining a MAP of 85-90 for first 7 days following ASCI "to improve spinal cord perfusion".

As is often the case, data from animal studies has been extrapolated to humans and has played a role in the development of these recommendations. There is a vast body of literature on animal models of ASCI and its management. Therefore, the first step in performing a comprehensive review of the literature and data on the management of ASCI should begin with a review of the animal study precursors which set the stage for later clinical studies.

The purpose of this review was to look at all the animal studies conducted which looked at hemodynamic parameters in animal models of ASCI and the effect of post-injury MAP on the neurological outcomes.

Methods:

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers was conducted. The data is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The review questions and search strategy were decided upon by the primary author (BS) and supervisor (NB).

Search Question, Population, Inclusion and Exclusion Criteria:

The question posed for systematic review was: What is the effect of post-injury MAP on functional outcome in animals with acute traumatic spinal cord injury? The functional outcome was defined as neurological exam (e.g. incline plane

test), motor evoked potentials (MEPs), spinal evoked potentials (SEP) and dorsal column evoked potentials (DCEPs).

Our inclusion criteria took into consideration the likely heterogeneity of the studies. We only included animal models of traumatic spinal cord injury. The studies had to address BP/ MAP/ Hemodynamic parameters directly. They had to document neurologic outcome/ recovery in relation to BP, with neurologic outcome measures being defined as physical exam or physiological studies (evoked potentials). All studies included had to have 5 or more experimental subjects.

We excluded all human studies. Studies looking exclusively at neuroprotective agents without documenting hemodynamic parameters were also excluded. Studies that did not address neurologic recovery/functional outcome were not included. Non-traumatic models (e.g. models for ischemia) were not a part of the inclusion criteria.

The primary outcome measure documented is effect of MAP on functional neurological outcomes, as defined by neurological exam (e.g. incline plane test), recovery/change in MEPs or SEPs. There were no specific secondary outcome measures for our review. Any secondary measures were documented as they appeared in each individual study. Secondary outcomes documented in parent studies included spinal cord blood flow (SCBF) as well as morphometric and histopathological studies. Some studies included in this review looked at the above mentioned secondary outcomes as their primary outcomes with neurological outcome being documented as a secondary outcome.

Search Strategy:

MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from inception to January 2015 were searched using our pre-conceived list of synonyms for "traumatic spinal cord injury", "spinal cord perfusion pressure" and "functional outcome". The search strategy for MEDLINE can be seen in Appendix A of the supplementary material, with a similar search strategy utilized for the other databases.

Meeting proceedings for the last 10 years were also searched, looking for ongoing and unpublished work based on MABP directed therapy to maintain spinal cord perfusion pressure in animal models of traumatic spinal cord injury. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation (CNSF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Neurosurgical Society (ENSS), World Federation of Neurological Surgeons (WFNS), American Neurology Association (ANA), American Academy of Neurology (AAN), European Federation of Neurological Science (EFNS), World Congress of Neurology (WCN), Society of Critical Care Medicine (SCCM), Neurocritical Care Society (NCS), World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), American Society for Anesthesiologists (ASA), World Federation of Societies of Anesthesiologist (WFSA), Australian Society of Anesthesiologists, International Anesthesia Research Society (IARS), Society of Neurosurgical Anesthesiology and Critical Care (SNACC), Society for Neuroscience in Anesthesiology and Critical Care, the Japanese Society of Neuroanesthesia and Critical Care (JSNCC), the North

American Spinal Society (NASS), the Canadian Spine Society (CSS), and the Eurospine Society.

Finally, reference lists of any review articles or systematic reviews on spinal cord perfusion pressure goals in acute traumatic spinal cord injury were manually searched for any missed articles.

Study Selection:

Utilizing two reviewers (BS + FZ), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they meet the inclusion criteria. Second, full text of the chosen articles were then assessed to confirm that they met the inclusion criteria and that they document functional neurological outcome post MAP directed therapy. Any discrepancies between the two reviewers were resolved by a third party (NB).

Data Collection:

Data was extracted from the selected articles and stored in an electronic database. Data fields include: species, number of subjects, study design, primary endpoints, trauma model, treatment/manipulation of MAP, duration of BP manipulation, outcome assessment technique, primary outcome and secondary outcome.

Statistics:

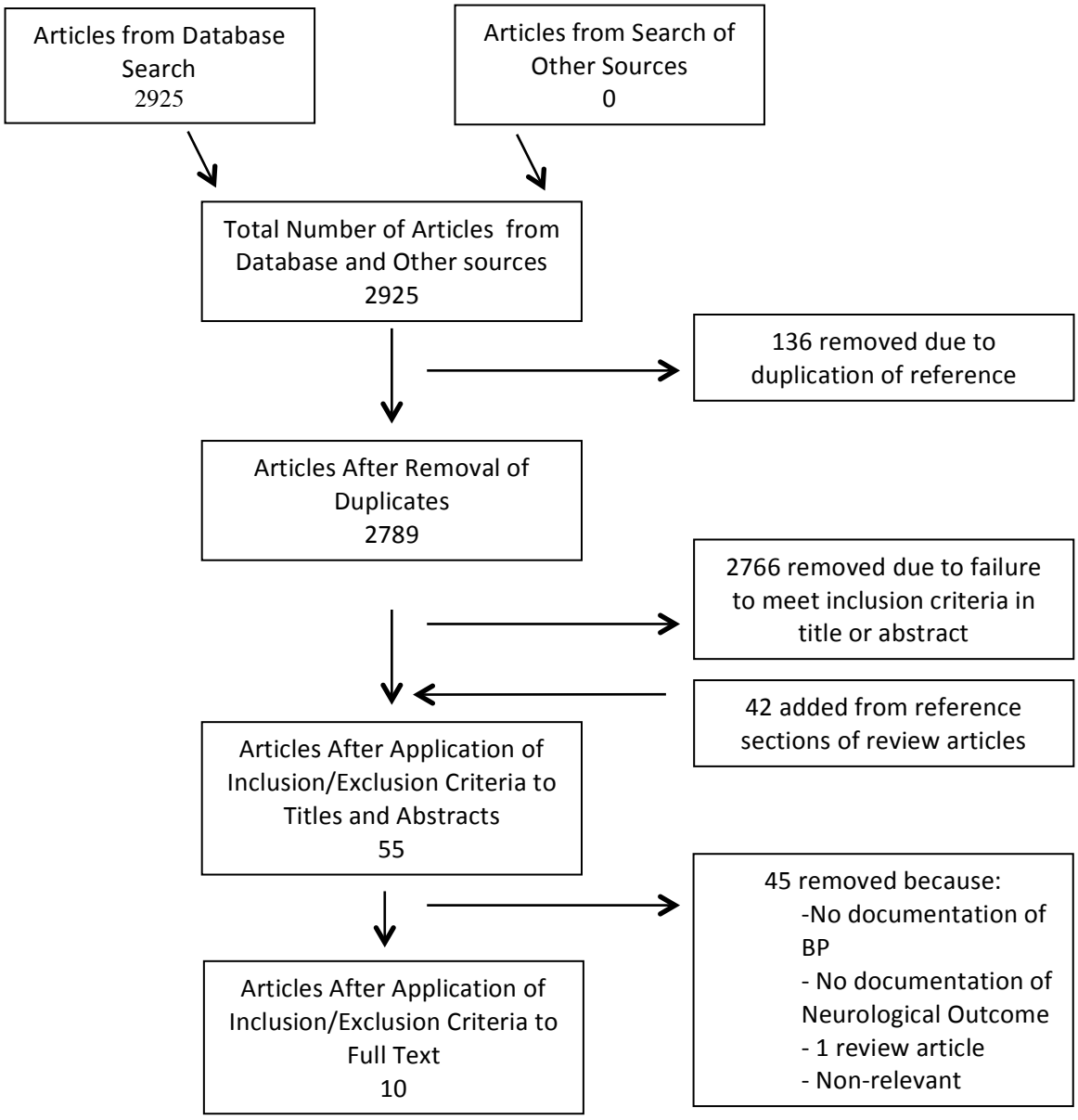
A meta-analysis was not performed in this study due to the heterogeneity of the data within the animal studies.

Results:

The above mentioned strategy yielded a total of 2925 total results from the databases and grey literature search. After manually removing the duplicates, we were left with 2789 results. A review of the titles, and when relevant, their abstracts, yielded 13 possible titles of interest. We then manually checked the references of these titles which yielded another 42 results of interest, bringing the total number to 55. All of these titles were then fully reviewed and 10 studies were selected based on our pre-determined inclusion and exclusion criteria.

Figure 1 demonstrates the results of the above listed search strategy:

Fig. 1: Search Results



Original Search:

Each synonym for the 3 variables combined with "or" operator; the results of these searches for each variable combined with "and", combining all three variables

Ovid, Embase, Globalhealth: 2004 results

Biosis: 165 results

Cochrane: 209 results

Scopus: 547 results

Total: 2925

Summary of Evidence:

Species:

There was a diverse selection of animals in the studies we obtained in our search. Lambs (1), dogs (2), cats (3), rats (2), pigs (1) and rabbits (1) were used.

Primary Outcome measures:

As mentioned above, we set out to find studies that documented some kind of neurological outcome either in the form of physical exam findings or physiological measures of evoked potentials. Predictably, the studies accumulated had diverse methods and techniques for documenting outcome measures.

SEP and DCEP measurement:

Of the 10 studies, 5 of them used SSEP or DCEP as a measure of neurological outcome. Dyste et al. (15) determined SEPs and SCBF at 0.5, 1, 1.5 and 2.5 hours after injury. Griffiths et al. (17) looked at SCBF and DCEP during subacute cord compression and studied the effect of progressive hypotension during cord compression. As a part of their outcome assessment, Hukuda et al. (14) looked at

SEPs before, immediately after and 30 minutes after SCI. They repeated measurement of SEPs at weekly intervals for 8 weeks after injury. Haghighi et al. (11) recorded SEPs at baseline, and immediately after trauma. Subsequent recordings were made every 5 minutes for up to 2 hours. Fehlings et al. (8) concomitantly measured SSEPs and MEPs while measuring SCBF. Recordings were performed immediately after therapeutic agent infusion and at 1 and 2 hours after cessation of drug delivery.

CEP measurement:

Of the studies obtained, 2 studies used cortical evoked potentials (CEPs) as a measure of neurological outcome. Hardy et al. (13) studied how increasing weight on the spinal cord affected CEPs and how a subsequent increase in MAP affected this conduction block. Similarly, Brodkey et al. (12) tried to demonstrate the interaction between the effects of pressure applied to the spinal cord and reduced arterial perfusion of the cord, as shown by effects on CEPs.

Neurological Exam:

Of the ten studies in this review, only 3 studies used a physical neurological exam to document neurological outcome. In addition to measuring SEPs, Hukuda et al. (14) did weekly neurological exams for up to 8 weeks. The strength of the dogs was graded on a 1 to 4 scale. Gambardella et al. (16) obtained neurological exams at 1, 24 and 48 hours post-injury. They used the Tarlov scale to document their

neurological exams. Dolan et al. assessed functional recovery on a weekly basis for 8 weeks after injury using the incline plane technique.

TABLE 1: Summary of Animal Data

Study	Species	# of Subjects	Study design	Primary End Points
Dyste et al. (1989)	Lambs	39	Anesthetized Lambs subjected to epidural cord compression at t13 at 200 mm hg for 80 minutes. 9 animals received hetastarch, 8 animals mannitol, 10 animals received phenylephrine to raise MAP by 20 to 40%. 12 control animals received saline. SEPs and SCBF determined at ½, 1 ½, 2 ½ hours after compression. Animals killed at 2.5 hours	Attempt to augment Spinal cord blood flow (SCBF) following cord injury, either with hetastarch, mannitol-induced volume expansion or phenylephrine induced hypertension
Griffiths et al. (1979)	Dogs	12	SCBF and dorsal column conduction, assessed by DCEP, were measured during subacute cord compression. Three groups. Group 1, 6 dogs, no manipulation of map. Increase in pressure in steps of 20 to 30 mm of hg. Group 2, 4 dogs, induced hypotension. Pressure increased in increments of 5 to 10 mm of hg and recordings made until conduction failure. Group 3, 2 dogs, Used to assess effect of progressive hypotension on DCEP. DCEP studied as MAP reduced.	Examine whether conduction defects caused by ischemia or other factors. Seconary: To study the interrelationships of SCBF, PP and cord conduction during focal compression
Hukuda et al. (1980)	Dogs	36	T5 and T6 laminectomy. Sudden inflation of 400 mm Hg a tourniquet that encircled the spinal cord epidurally. This inflation pressure maintained for 5 min. SEPs recorded before, immediately after and 30 min after trauma. Half dogs intermittent hypertension and hypercarbia, which consisted of 15 min of hypertension and 95% O2 5% CO2 gas ventilation and 170-200 mm HG induced by IV norepinephrine. This was alternated with 10 minutes of normotensive	Assess the therapeutic effects of combined hypertension and hypercarbia against acute spinal cord trauma

			air ventilation for 3 hours, beginning 3 hours after injury. Remainder of dogs were controls. Neurological and SEP examinations repeated at weekly intervals up to 8 weeks	
Hardy et al. (1972)	Cats	7	Abolishing cortical evoked potential by applying increasing weight to the spinal cord. The effects of raising the blood pressure on the CEPs were then assessed.	To determine the effect of hypertension on conduction block secondary to compression
Brodkey et al. (1972)	Cats	5	Applied weight to spinal cord and also decreased the BP in abdominal aorta first separately, then both forms of trauma at same time. Each mode of trauma was first applied separately for 15-30 min. When it was shown that it alone would not affect CEP, the other mode was added and the time to the block of the CEP was noted. After the block of the CEP was demonstrated, the first mode of trauma was removed and the time required for the CEP to return was recorded. Then experiment repeated but in reverse order. In last two cats, only one block produced.	To demonstrate interaction between the effects of pressure applied to the cord and of reduced arterial perfusion of the cord; as shown by effects on CEP
Haghighi et al. (1988)	Cats	10	Spinal evoked responses were abolished after weight drop injury of 100g-cm. 5 cats were treated with nimodipine and 5 cats were treated with saline. Both groups received equal volumes of fluid. SEPs were recorded at baseline, and immediately after trauma. Subsequent recordings were made every 5 minutes up to 2 hours.	To evaluate the effect of nimodipine in functional recovery of the spinal cord as measured by SEPs
Gambardella et al. (1995)	Rabbit		5 groups, 16 in each group. T12- L1 laminectomy. Spinal cord injury induced with modified Sujita vascular clip. Group 1: Anesthetized and subjected to all procedures but no spinal cord injury and no pharmacological	To assess the effect of combination of nimodipine and adrenaline treatment on neurooutcome and morphometric axonal changes following secondary spinal cord damage. Neurooutcome measured using Tarlov scale

			treatment. Group 2: spinal cord compression 2 min and 5 min. 8 in each subgroup. Received normal saline. Group 3: same division as group 2. Received nimodipine (1.5 mcg/kg/min iv for 2 hours) Map maintained near control levels with adrenaline. Group 4: Same division and group 2 and 3. Nimodipine alone, same dose as above for 2 hours. Group 5: same division as group 2 and 3. Adrenaline alone for 2 hours, same dose as group 3. To maintain MAP near control. Neuroexam performed at 1, 24 and 48 hours after the end of spinal cord compression.	
Dolan et al. (1980)	Rats	36	Acute spinal cord compression at T1 by a 180 gram clip for one minute; this produced profound hypotension. Three groups:Untreated animals served as controls, Normotensive group with MAPs kept between 100 and 120 mm of hg, and hypertensive group with MAPs maintained between 125 and 150 mm of Hg. MAP raised for one hour after injury. Functional recovery assessed weekly for eight weeks post-operatively by the inclined plane method	To assess long term functional value of elevating systemic blood pressure after spinal cord injury. Functional recovery of treated animals compared to that of untreated hypotensive animals
Barrios et al. (2014)	Pig	15	Surgical procedures under general anesthesia. Spinal cord and nerve roots exposed from T6 to T10. 3 groups, 5 subjects per group. Separation group(cord translation), root stump pull and torsion groups. An electromechanical external device was used to apply the displacing forces. The three displacement forces were repeated after sectioning the adjacent nerve roots. The experiments were then carried about under	To determine the limits of cord displacement before disappearance of neurophysiologic signals. Influence of type of force, section of the roots and induced hypotension on cords tolerance also assessed

			induced hypotension.	
Fehlings et al. (1989)	Rats	30	30 adult wistar rats were anesthetized. Laminectomy was made from C6 to T2 and each rat received 1 minute extradural clip compression injury of the cord at T-1 with modified aneurysm clip a force of 53 gm. SCBF was measured by hydrogen clearance technique. MEPs and SSEPs were concomitantly recorded with the SCBF. Rats were randomly and blindly assigned to the following groups (5 per group): placebo and saline, placebo and dextran 40, nimodipine 0.02 mg/kg and saline, nimodipine 0.02 mg/kg and dextran 40, nimodipine 0.05 mg/kg and saline, and nimodipine 0.05 mg/kg and dextran 40. Two Harvard infusion pumps were used to deliver a fixed volume of drug at a constant rate over 1 hour; post infusion SCBF and EP recordings were made immediately following the infusion and at 1 and 2 hours after cessation of drug delivery	To assess whether administration of nimodipine and dextran 40, either alone or in combination, could increase posttraumatic SCBF and improve axonal function in the cord after acute SCI

Abbreviations

MAP: Mean Arterial Pressure, SCBF: Spinal cord blood flow, DCEP: Dorsal Column evoked potential, SEP: Spinal evoked potential, SCI: Spinal Cord injury, CEP: Cortical evoked potential

TABLE 2: Summary of Animal Data

Study	Trauma Model	Treatment; Manipulation of MAP	Duration of BP manipulation/ intervention	Outcome assessment technique
Dyste et al. (1989)	Epidural balloon inflated and maintained at 200 mm Hg for 80 minutes with a syringe pump	9 animals received hetastarch 20 ml/kg IV bolus of 6% solution followed by maintenance infusion at 80 ml/hr; 8 animals mannitol at 1 g/kg IV bolus of 20% solution followed by an infusion of 1g/kg/hr ; 10 animals received phenylephrine; they received an IV infusion of a 16% solution of PE at a rate sufficient to raise and maintain MAP by 20 to 40% over the compression MAP ; 12 control animals received saline at 80ml/hr.	Entire experiment (2.5 Hours)	Bipolar electrodes at C7 and L7 to stimulate and to record SEPs. SCBF was measured using the radiolabelled microsphere technique. SEPs and SCBF determined at ½, 1 ½, 2 ½ hours after compression
Griffiths et al. (1979)	Ventral, midline balloon compression at L2	Map reduced and maintained at 70 to 80 mm Hg in groups 2 and 3 using trimetaphan camsylate and sodium nitroprusside	Until conduction failure; time not specified	DCEP assessed. Hydrogen gas technique used to measure SCBF.
Hukuda et al. (1980)	Inflation of tourniquet that encircled spinal cord epidurally to 400 mm of hg; pressure maintained for 5 minutes. Injury produced at T5-T6 level	3 hours after injury, 15 min of hypertension and 95% O2 5% CO2 gas ventilation were alternated with 10 minutes of normotensive air ventilation; MAPs maintained at 170-200 mm hg and was induced with IV infusion of 0.002% norepinephrine	3 hours	Neurological Exam (Grade 1-4) as well as SEP repeated for up to 8 weeks; The thoracic cords were examined pathologically at the end of the experiment, comparing the size of hemmorragic lesions in control and treatment groups
Hardy et al. (1972)	Increasing weight to the spinal cord (38-53 g)	MAP raised to 150-200 mm Hg with 1-2 mg levarterenol bitartrate	30-60 min	CEP measurement
Brodkey et al. (1972)	Clamp on thoracic Aorta to reduce perfusion pressure. Low thoracic laminectomy, weight holding apparatus positioned to deliver weight (18 to 38 gm) over entire dorsal surface of cord and intact dura.	MAP reduced to 60 mm Hg in thoracic aorta while weight was applied to spinal cord	Bp maintained low until disappearance of CEPs	Time to return of CEP
Haghighi et al. (1988)	Weight drop model; 100 g-cm impact injury	5 cats were treated with nimodipine; 10	2 hours	Recovery of SEPs

	at T-13 using modified Allen's trauma device	mcg/kg bolus followed by 1mcg/kg/min infusion. 5 cats were treated with saline. Both groups received equal volumes of fluid. Nimodipine treated group had MAPs significantly less than saline group (P<0.05) (MAPs dropped by 32% compared to baseline)		
Gambardella et al. (1995)	Modified Sujita vascular clip applied at T12-L1 level; applied perpendicular so that a 60.5 to 64.2% reduction in diameter in order to cause incomplete spinal cord injury. The clip was left on for 2 and 5 minutes in the trauma groups	Group 1: No injury, no pharmacological treatment Group 2: Received NS post injury Group 3: Received nimodipine (1.5 mcg/kg/min iv) Map maintained near control levels with adrenaline (1:100000 solution saline; 40 drops/min) Group 4: Nimodipine only same dose as above Group 5: Adrenaline only, same dose as above to maintain MAPs at control levels Cord Compression decreased MAP to 81 +/-3.5 in all animals; NS did not restore bp to control levels; Treatment with Nimodipine alone decreased bp further by 20-40 mm Hg. MAP maintained within physiological limits (120 mm Hg) in adrenaline alone and adrenaline + nimodipine groups	2 hours	Neurological outcome was evaluated by comparing scores obtained with Tarlov scale at 1, 24 and 48 hours after the end of spinal cord compression; Morphometric studies were carried out 48 hours after injury; the number of myelinated axons per unit area was compared in the groups
Dolan et al. (1980)	Modified aneurysm clip exerting compression force of 180 g for one minute at T1	Normotensive group with MAPs kept between 100 and 120 mm of hg, and hypertensive group with MAPs maintained between 125 and 150 mm of Hg using sufficient noradrenaline; stopping infusion in treated animals after 60 minutes caused an immediate fall in the mean bp to levels below those of control animals (mean of 76 +/-1 mm Hg in	Noradrenaline was infused for 60 minutes, then bp was monitored for 15 minutes	Functional recovery assessed weekly for 8 weeks after injury using inclined plane technique

		Normotensive and 77+/-1 in hypertensive group compared to 84+/-2 in control)		
Barrios et al. (2014)	Cord Translation group, root stump pull group and torsion group. Electromechanical device used to apply displacing forces. Procedures performed at the T6 to T10 level	Induced hypotension to MAP of 45 mm hg (50% decrease from the baseline MAP in pigs) using 0.1 to 0.5 mg esmolol, followed after 2 minutes by nitroprusside sodium at 0.001 to 0.01 mg/min	Until loss neurophysiologic signals (exact duration of hypotension unspecified)	Direct cord-to-cord evoked potentials recorded. Amount of displacement of cord until disappearance of CCEPs was measured for each group with unharmed roots, severed roots and under induced hypotension
Fehlings et al. (1989)	Modified aneurysm clip; 1 minute of 53 gm of extradural compression at T-1	MAPs not directly manipulated but they were measured in the different groups; MAPB was significantly increased ($p<0.02$) following infusion of placebo and saline (74+/- 8.3), placebo and dextran 40 (85 +/- 7.7 mm hg) and nimodipine 0.02 mg/kg and dextran 40 (88.4 +/- 8.4 mm Hg). However, at 1 hour after drug infusion, the MABP was again similar among the six treatment groups ($p>0.05$)	1 hour	MEPs and SSEPs were recorded concomitantly with the SCBF 1 hour before and at 1, 2, 3 and 4 hours after SCI.

Abbreviations

MAP: Mean Arterial Pressure, SCBF: Spinal cord blood flow, DCEP: Dorsal Column evoked potential, SEP: Spinal evoked potential, SCI: Spinal Cord injury, CEP: Cortical evoked potential

TABLE 3: Summary of Animal Data

Study	Primary Outcome	Secondary Outcome	Biases/ Shortcomings	Overall Impression
Dyste et al. (1989)	Hetastarch group: Spinal cord blood flow not affected at any cord segment Mannitol: Did not affect blood flow to any measured tissue Phenylephrine: SCBF significantly greater than the baseline level at 30 min after compression ($p<0.05$) but not at subsequent measures of flow Regression analysis showed only PE group was statistically significant predictor of SCBF	MAP was highest in PE group after initiation of treatment compared to all other groups and was statistically significantly different from control group (<0.01). Within 10 minutes of balloon inflation, the SEPs were obliterated. There was no recovery of SEP during the remainder of the experiment in any treatment group, including PE group.	SEP data recorded during experiment do not give an accurate prediction of long-term outcome;	In PE group, despite having MAPs higher than control group (MAP kept at baseline) and other groups, there was no difference in neurological recovery. Negative study.
Griffiths et al. (1979)	In group 1 (normotensive), the SCBF remained unchanged until a PP of 65 to 70 mm Hg. Below that pressure, flow declined and was 50% of control values at PP of 35 mm Hg. For cord pressures, Flow remained constant until cord pressures increased to 55 to 60 mm Hg above which it declined. In group 2(hypotensive), the flow started to decrease at PP of 70 mm Hg, which corresponded to cord pressures of 15 to 20 mm Hg. Amplitude of the DCEP decreased significantly from control at each reduction of PP in both groups. In group 1 conduction failure occurred at cord pressures of 90 to 100 mm Hg and PP of 20 to 30 mm Hg. In group 2 conduction failure occurred when PP measured 30 to 40 mm Hg and cord pressures were 20 to 40 mm Hg. There was no	MAP was significantly different between groups 1 and 2 (125+/- 8 in group 1, 71+/- 14 in group 2, $p<0.01$); Cord pressure was significantly different as well (Group 1 96+/- 5 , group 2 28+/-11) however no difference in SCBF or PP.	Only twelve subjects in entire study. No actual neurological exam performed on subjects to assess neurological outcome. No long term follow up which may be necessary in spinal cord injury.	DCEP conduction failure occurred at a higher PP in hypotensive group; may suggest some benefit to keeping subjects normotensive, but not sufficient evidence to support normotensive or hypertensive support

	significant difference in SCBF or PP between the two groups, but the level of PP at conduction failure was higher in Group 2. Group 3(hypotension only) reduction in amplitude of DCEP by 12% when PP reduced to 43 mm Hg. At these lower levels of PP the amplitude of DCEP is greater than in Group 1 and 2.			
Hukuda et al. (1980)	During first week, treated dogs attained better neurological grades but was not statistically significant. After first week, both groups demonstrated steady neurological improvement for next 2 weeks but remained paraparetic thereafter. There was no significant difference when comparing sizes of spinal cord lesions between treatment and control groups	SEP recovered in some dogs in both control and treatment groups. There was no difference observed in recovery rate between the treatment group and the controls. However those dogs (from either group) in which SEPs recovered also attained better neurological grades($p<0.001$) and had smaller pathological lesions ($p<0.001$) compared to those who had no recovery of SEPs	Lack of follow-up SEP study in half of the dogs made the analysis somewhat inaccurate; treatment initiated 3 hours post-injury which may be too late for recovery of damaged neurons	Despite hypertensive therapy, treated dogs did not have a better neurological outcome compared to controls. Negative study.
Hardy et al. (1972)	When bp was raised to 150-200 mm Hg, the CEP returned in 2-5 min. The CEP was lost when bp returned to normal in 5-18 min.	None	Only 7 subjects; Neurological function not examined, only CEPs looked at; duration of study only 60 min, no long term outcome assessment; the actual data of each individual subject not displayed	Recovery of CEP with raised bp; insufficient evidence to support hypertensive therapy.
Brodkey et al. (1972)	Effects of pressure and ischemia are additive when CEP is concerned;	In two of the cats, after CEP had disappeared due to combined effects of weight and bp reduction, weight was removed and potential returned but disappeared again after 5 and 15 minutes. When bp raised to normal levels CEP promptly returned and did not disappear again when bp was subsequently reduced after 30 mins of normotension	Only 5 subjects; in 2 of the 5 subjects, only single block applied. Only CEP used, no neurological exam performed	Some suggestion that maintaining normotension in post injury period may be beneficial for CEP recovery
Haghighi et al. (1988)	In control (Saline) group, average time to return of SEPs post injury was 50+/- 15 minutes. In	Spinal cord specimens used to document location of trauma to cord; histological changes were mild in all	Not specifically looking at effects of MAP on neurological recovery; trying to determine neuroprotective effects of	Clear suggestion that hypotension in post injury period detrimental for neurological

	nimodipine treated cats, 3 did not show return of SEPs up to 4 hours posttrauma. Of the remaining 2, SEPs returned on average 80 +/- 10 minutes.	cases and did not correlate with outcome	nimodipine	outcome.
Gambardella et al. (1995)	In all animals, cord compression induced 5th degree deficit. Saline improved the motor deficit slightly. Adrenaline alone groups showed a better recovery in comparison with animals treated with saline alone. Nimodipine +adrenaline group showed the most improvement in neurological outcome. The groups that showed most improvement were those with higher MAPs (kept at baseline of 120 mm Hg)	Morphometric Studies showed axonal number was significantly ($p<0.05$-0.001) reduced in all groups subjected to spinal cord injury when compared to control group. In the group of animals treated with a combination of nimodipine and adrenaline, the concentration of axons in the regions of trauma or a region caudal to it was greater than in the other group of animals.	Possible protective effects of nimodipine may confound results when comparing nimodipine+adrenaline group to control group; duration of experiment only 48 hours which may not be enough time to for full neurological recovery.	Better neurological outcomes in treatment groups where MAPs were maintained at baseline (MAPs 120 mm Hg, normotensive). Hypertensive therapy not looked at.
Dolan et al. (1980)	Weekly mean inclined plane values for 8 weeks showed no statistically significant difference between the three groups at any time after injury	None	Hypotension which occurred after 60-minute infusion was discontinued may have had negative effects, off setting any improvement caused by infusion. 60 minutes of treatment may have been insufficient duration for treatment. Subjects may need longer MAP support for potential recovery.	No difference in neurological outcome in hypertensive vs normotensive vs control groups. Negative study.
Barrios et al. (2014)	Group 1: Separation group. Evoked potential disappeared with a displacement of 10.1 +/- 1.6 mm with unharmed roots and 15.3 +/-4.7 mm after sectioning of 4 adjacent roots ($p<0.1$). After induced hypotension potentials lost at 4.0 +/-1.2 mm ($p<0.1$). Group 2: Root stump pull: absence of potentials occurred at 20 +/- 4.3 mm and increased to 23.5+/- 2.1 mm ($p<0.5$) after cutting the two contralateral roots. With induced hypotension signals	Pathological study performed showed that independently from the spinal cord displacement method, none of the spinal cord samples showed macroscopic, histologic or immunohistochemical damage	Cord manipulation took place immediately after decrease in MAP, which may not have allowed for spinal cord autoregulation. The sacrifice of the roots under hypotensive conditions may have affected the cord vascularization. Return of signal was not correlated with neurological function.	Clear suggestion that cord does not tolerate manipulation under hypotensive conditions. Hypertensive conditions not looked at.

	lost at 5.3+/-1.2 mm ($p<0.1$). Group 3: Torsion group. Cord allowed torsion of 95.3+/-0.2 degress that increased to 112.4 +/- 7.1 ($p<0.1$) degrees if contralateral nerve roots cut. Under hypotension, loss of potentials at 20+/-6.2 degrees ($p<0.1$).			
Fehlings et al. (1989)	Only the combination of nimodipine 0.02 mg/kg and dextran 40 increased SCBF at T-1 (43.69 +/- 6.09 ml/100gm/min; $p<0.003$) and improved MEPs and SSEPs following SCI	Histopathology revealed that neither the total volume of hemorrhage at the injury site ($p>0.05$) nor the percent hemorrhage by volume ($p>0.05$) varied significantly among treatment groups	Interventions were not directly targeting bp; the duration of the interventions were only 1 hour; 1 hours after injury the MABP in all groups were similar; only 4 hour duration of experiement	Despite having MABP that was higher in placebo and saline groups, placebo and dextran 40 groups compared to nimodipine 0.02 mg/kg and saline, nimodipine 0.05 mg/kg and saline and nimodipine 0.05 mg/kg and dextran 40 groups, there was no improvement in neurological outcome. In this scenario MABP by itself did not contribute to neurological improvement.

Abbreviations

MAP: Mean Arterial Pressure, SCBF: Spinal cord blood flow, DCEP: Dorsal Column evoked potential, SEP: Spinal evoked potential, SCI: Spinal Cord injury, CEP: Cortical evoked potential

Discussion:

It is a currently employed therapeutic practice in many institutions to target high MAPs immediately after spinal cord injury in order to reduce the amount of secondary injury as well as improve neurological outcome. The targeting of MAPs and SBP after ASCI is still a controversial subject, as there exists little evidence to

support the current treatment recommendations. Current recommendations of keeping MAP above 85-90 is based on level III evidence only. The reasoning behind this suggestion is that maintaining spinal cord perfusion immediately post-injury is important to reduce the effects of secondary injury that follows the initial insult. To our knowledge, there is no systematic review of the animal studies on which these recommendations are based. The purpose of this review was to accumulate all of the animal data available that addresses post-injury MAPs and SBP and try to assess the validity of these recommendations.

We limited our inclusion criteria to studies that actually measured some sort of neurological outcome, either by physical exam or with electrophysiological evidence. We purposefully excluded studies which only addressed spinal cord blood flow only, in order to better correlate the effect of MAP with actual clinical outcomes.

Our search strategy yielded 10 studies that met our inclusion criteria. It is not surprising that we found studies with significant heterogeneity. There were significant differences in study population, method of inducing injury, method of manipulating MAP/SBP and measuring neurological outcome. Given these differences, a statistical analysis and regression model was deemed to be unhelpful.

Of the 10 studies that our search strategy yielded, 4 could be considered to be "positive studies" (12,13,16,17); these were actually studies that showed some neurological improvement or beneficial effect to having the blood pressure manipulated. The studies performed by Griffiths et al, Brodkey et al. and Gambardella et al. all showed improved neurological outcome when the blood

pressure was manipulated and maintained at a normotensive level. Hardy et al. was the only study that showed a benefit of maintaining the systemic blood pressure at a hypertensive level.

The studies performed by Barrios et al. (10) and Haghighi et al. (11) showed evidence that hypotension in the immediate post-injury period was detrimental to neurological outcome. These studies did not address hypertensive conditions in the post-injury period, as these the primary goal of these studies was not the impact of blood pressure in the immediate post-injury period.

The remaining four studies (8,9,14,15) yielded by the search strategy can be classified as "negative studies". These studies demonstrated no benefits of higher MAPs compared to control groups in the immediate post-injury period. The control groups in these studies consisted of hypotensive and normotensive groups as a comparison. Despite having higher MAPs, none of these studies demonstrated a statistically significant difference in neurological recovery.

Due to the heterogeneity of these studies, no definitive conclusion can be reached regarding the impact of MAP on neurological outcome in ASCI models. However, we did make certain observations; first of all, in the positive studies mentioned, there is only one study which shows a positive outcome for hypertension (13). The other 3 studies show a benefit of maintaining normotension as opposed to pushing the MAPs to a supraphysiological level. In fact, there is evidence which suggests that hypertension causes larger hemorrhage and edema in the spinal cord at the level of injury as well as the adjacent levels due to loss of autoregulation(19). Secondly, two studies on our list (10,11) invariably showed that

hypotension in the setting of ASCI is most likely detrimental to the neurological outcome. This is not surprising, as hypotension has been shown to be harmful in the setting of acute traumatic brain injury as well (20) and should be avoided in these patients.

The negative studies yielded in our search failed to show any benefit for higher MAPs on neurological outcome. The main critique of these studies is usually two-fold; firstly, the blood pressure was manipulated for a period of hours only. Proponents of hypertension in the post-injury period argue that in order to prevent secondary injury, the blood pressure should be maintained elevated over period of days (6,7), which was based on an experimental animal SCI study that showed that between days 3 and 5 after injury, the spinal cord experienced the greatest degree of cord edema and vascular congestion (21). Secondly, the neurological outcome is also assessed after a period of hours at the end of the experiment. Most will argue that this is insufficient time for neurological recovery to occur after a severe ASCI and that a more accurate assessment of neurological recovery would be after a period of weeks to months, when the damaged neuronal structures have had time to recover. Dolan et al. assessed functional recovery at the 8 week mark and did not find any difference between the normotensive, hypertensive and control groups. However, they only manipulated the MAPs over a 60 minute period.

Limitations:

This review was not without its limitations. The heterogeneity of the studies compiled is perhaps one the main causes of the limitations. There were different

animals used in most of the studies found; it is difficult to say what the impact of this species variation is on the response to manipulation of the MAP. Different mechanisms were used to induce traumatic SCI, and these different mechanisms can potentially lead to different secondary injury cascades, making it difficult to generalize results obtained. Heterogeneous outcome assessments made it difficult to come to an overall conclusion about the impact of MAP on functional outcome. Also notable is the small number of studies we were able to obtain within the confines of our search; these studies did not contain a large number of experimental studies either, further limiting our ability to come to any certain conclusions. Given that these were animal studies, even if the above stated limitations did not exist, we would not be able to extrapolate these results to humans.

Conclusion:

This review concludes that within the animal literature, there is insufficient evidence to draw a conclusion about the effect of MAP on neurological outcome in animal models of ASCI. However, it is perhaps safe to assume that hypotension leads to unfavorable outcomes and should be avoided. The role of induced hypertension in the immediate post-injury period requires further study, as this treatment is not without risk.

As previously mentioned, a review of the animal literature was the first logical step in studying MAP in the setting of ASCI, as an important part of the clinical guidelines are derived from this literature. Having performed a scoping review of the animal literature in the context of our specific question, we moved on to look at the human literature available, which will be discussed in Chapter II.

Chapter II

Human Studies

The Impact of Mean Arterial Pressure on Functional Outcome Post-Acute Spinal Cord Injury: A Systematic Review

Introduction:

The management of acute spinal cord injury (ASCI) is a much debated and often controversial subject. Experimental evidence suggests that after the initial episode of cord injury and compression, there is an active secondary phase of injury (1,2). Secondary injury mechanisms include vascular changes such as reduction in blood flow, loss of autoregulation, neurogenic shock, hemorrhage, loss of microcirculation, vasospasm and thrombosis. Prevention of secondary injury in the immediate aftermath of ASCI is considered to be critical in improving neurological outcomes in this patient population. Augmentation of mean arterial pressure during the first 7 days post-injury is considered to aide in prevention of secondary injury, despite a lack of concrete evidence. Current AANS guidelines claim that there is insufficient evidence to support treatment guidelines. The "options" given include maintaining a MAP of 85-90 for first 7 days following ASCI "to improve spinal cord perfusion" (18).

This review is a follow-up to our previously written article which looked at animal models and the role of mean arterial pressure (MAP) in the period immediately following ASCI in experimental models and the associated outcomes. In this review, we look at how MAP manipulation in the immediate period following ASCI influenced neurological outcomes in a clinical setting.

Methods:

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers was conducted. The data is reported following

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The review questions and search strategy were decided upon by the primary author (BS) and supervisor (NB).

Search Question, Population, Inclusion and Exclusion Criteria:

The question posed for systematic review was: What is the effect of post-injury MAP on functional outcome in patients with acute traumatic spinal cord injury?

Our inclusion criteria took into consideration all prospective and retrospective adult and pediatric human studies/series with five or more patients with ASCI who presented to hospital and had documented neurological exams and outcomes. The studies had to address BP/ MAP/ Hemodynamic parameters directly. They had to document neurologic outcome/ recovery in relation to BP, with neurologic outcome measures being defined as a neurological exam documented as a scale or score which could be compared to the initial presentation (ASIA grade, ASIA motor score etc).

We excluded all experimental/animal models. Studies looking exclusively at neuroprotective agents without documenting hemodynamic parameters were also excluded. Studies that did not address neurologic recovery/functional outcome were not included.

The primary outcome measure documented is effect of MAP on functional neurological outcomes, as defined by neurological exam and the associated grade or scoring systems. There were no specific secondary outcome measures for our

review. Any secondary measures were documented as they appeared in each individual study. For each individual study, level of injury, complete vs incomplete injury, method and duration of MAP manipulation and method of outcome measures were also documented.

Search Strategy:

MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from inception to January 2015 were searched using our pre-conceived list of synonyms for "traumatic spinal cord injury", "spinal cord perfusion pressure" and "functional outcome". The search strategy for MEDLINE can be seen in Appendix A of the supplementary material, with a similar search strategy utilized for the other databases.

Meeting proceedings for the last 10 years were also searched, looking for ongoing and unpublished work based on MAP directed therapy to maintain spinal cord perfusion pressure in a clinical setting after patients had been admitted to hospital with ASCI. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation (CNSF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Neurosurgical Society (ENSS), World Federation of Neurological Surgeons (WFNS), American Neurology Association (ANA), American Academy of Neurology (AAN), European Federation of Neurological Science (EFNS), World Congress of Neurology (WCN), Society of Critical Care Medicine (SCCM), Neurocritical Care Society (NCS), World Federation of Societies of Intensive and

Critical Care Medicine (WFSICCM), American Society for Anesthesiologists (ASA), World Federation of Societies of Anesthesiologist (WFSA), Australian Society of Anesthesiologists, International Anesthesia Research Society (IARS), Society of Neurosurgical Anesthesiology and Critical Care (SNACC), Society for Neuroscience in Anesthesiology and Critical Care, the Japanese Society of Neuroanesthesia and Critical Care (JSNCC), the North American Spinal Society (NASS), the Canadian Spine Society (CSS), and the Eurospine Society.

Finally, reference lists of any review articles or systematic reviews on spinal cord perfusion pressure goals in acute traumatic spinal cord injury were manually searched for any missed articles.

Study Selection:

Utilizing two reviewers (BS + FZ), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they meet the inclusion criteria. Second, full text of the chosen articles were then assessed to confirm that they met the inclusion criteria and that they document functional neurological outcome post MAP directed therapy. Any discrepancies between the two reviewers were resolved by a third party (NB).

Data Collection:

Data was extracted from the selected articles and stored in an electronic database. Data fields included study design, number of patients, level of injury,

primary endpoints, duration of follow-up, complete vs incomplete injury, method and duration of MAP manipulation, outcome assessment measures and primary and secondary outcomes.

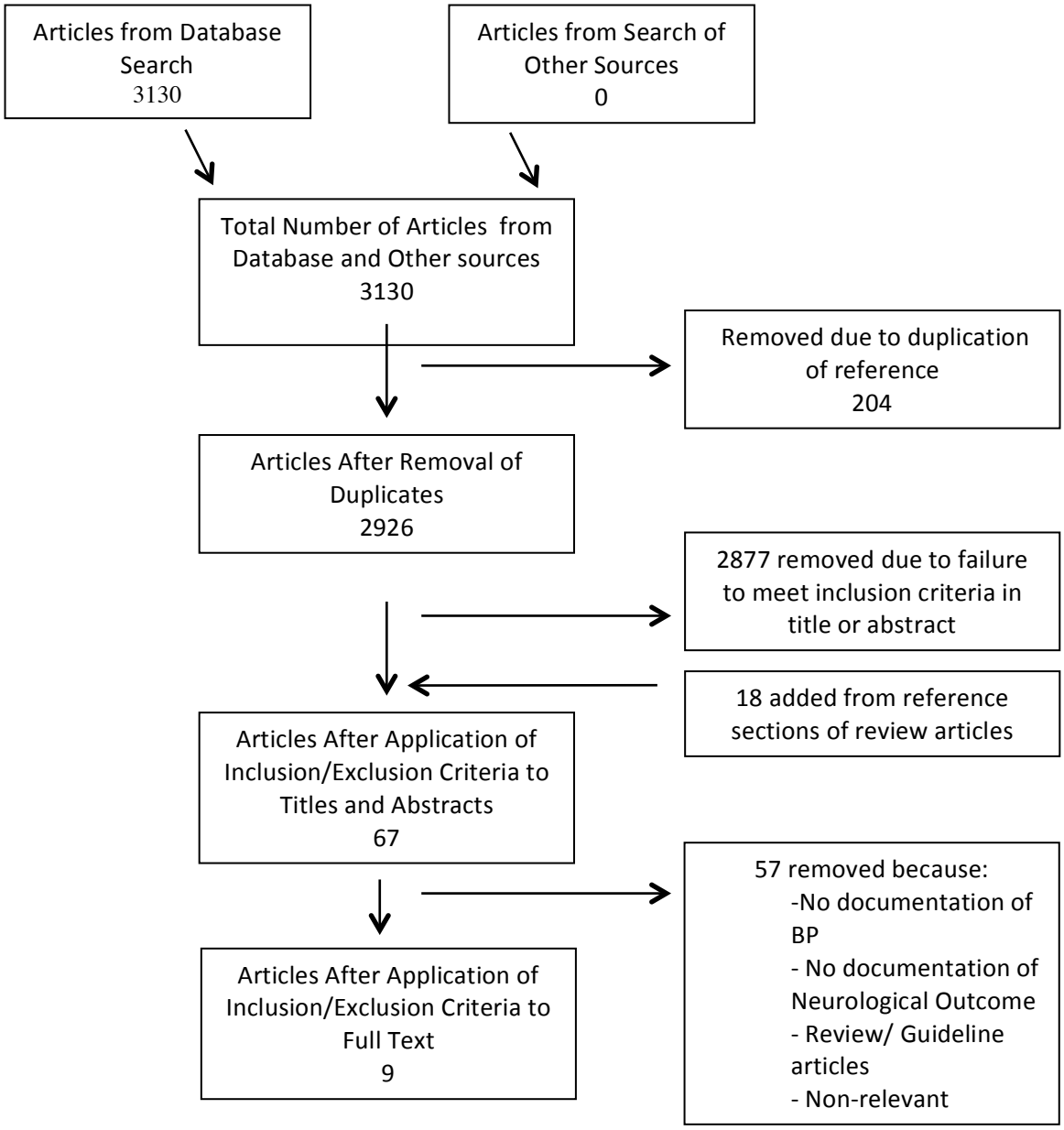
Statistics:

A meta-analysis was not performed due to the heterogeneity of the papers yielded by our search strategy.

Results:

The above mentioned strategy yielded a total of 3130 total results from the databases and grey literature search. After manually removing the duplicates, we were left with 2926 results. A review of the titles, and when of interest, their abstracts, yielded 49 possible titles of interest. We then manually checked the references of these titles which yielded another 18 results of interest, bringing the total number to 67. All of these titles were then fully reviewed and 9 studies were selected based on our pre-determined inclusion and exclusion criteria.
Figure 2 demonstrates the results of the above listed search strategy:

Fig. 2: Search Results



Original search:

Each synonym for the 3 variables combined with "or" operator; the results of these searches for each variable combined with "and", combining all three variables. After removal of duplicates, each database yielded the following:

Ovid, Global Health, Embase: 2070

Cochrane: 231

Biosis :166

Scopus: 459

Summary of Evidence:

Level of Injury:

Of the 9 papers that were looked at, 4 of them contained only patients with cervical injury (23,24,7,27). Two papers (6,26) looked at C and T spine injuries. Three papers contained patients with injuries of the C, T and L spine (22,25,28).

Study Design:

The papers looked at were predominately retrospective in nature. Only two papers (6,7) were prospective studies. The number of patients looked at in each study included in this review ranged from 17 to 131.

Outcome Measures:

ASIA grade:

ASIA grade (A to E) was used as an outcome measure by 4 of the 9 studies which were looked at. Hawryluk et al. (22) looked at improvement in ASIA grade from admission to ICU until discharge. There was no long-term follow up noted.

Readdy et al. (27) had the same outcome measures, with no long-term follow up. Inoue et al. (25) looked at ASIA grade only in the acute stage of hospitalization and did not document long-term follow up. Vale et al. (6) looked at improvement of ASIA grade and had follow-up exams performed at 6, 12 and 18 months after injury. Mean duration of follow-up was 17 months.

ASIA motor score:

Asia motor score was used as an outcome measure in 4 of the 9 studies as well. Cohn et al. (23) looked at ASIA motor index from first post-injury neurological exam and compared it to neurological exam before discharge. The duration of follow-up was from admission to discharge, with an average length of stay of 22 days. Martin et al. (26) also looked at this outcome measure during the acute hospitalization period only. In their study, the average length of admission was 18 +/- 13 days. Levi et al. (7) used the ASIA motor score as one of their outcome measures (they also used Yale motor score and Frankel score). They calculated percentage change in the scores mentioned, from admission until death or 6 weeks post-discharge. Kepler et al. (28) looked at change in ASIA motor score for the first 5 days after admission.

Frankel score and Yale motor score:

Wolf et al. (24) looked at Frankel score of Benzel and Larson as well as Yale motor scale. These scores were used to compare patients on presentation and at follow-up, which was at 3,6, 9 and 12 months post-injury. As mentioned above, Levi

et al. (7) also used the Frankel and Yale motor scores in addition to the ASIA motor score for their outcome assessment.

Table 4: Summary of Human Data

Study	Level of injury	# of Subjects	Study Design	Primary endpoints/ Follow up duration
Hawryluk et al. (2015)	C,T and L	74	Retrospective analysis of ASCI patients admitted to level 1 trauma center between 2005 and 2011, who were admitted to ICU for 5 days and MAP of at least 85 mm Hg was targeted. Computerized data acquisition at patients bedside in neurosurgical ICU. MAP measurements were collected at 1 minute intervals. Average MAP values were looked at during admission period, as well as looking at amount of time spent with MAPs below certain threshold values (40 to 120 mm Hg)	Change in Neurological status based on change in AIS grade at time of discharge compared to admission to ICU; F/u from admission to discharge. No longterm f/u
Wolf et al. (1991)	C spine only	52	Retrospective analysis of patients presenting to a single trauma center between July 1987 and December 1990, with bilateral facet dislocations. All of these patients were treated with their standardized protocol including simultaneous assessment and treatment of other injuries, intensive and invasive monitoring of vital signs, and hemodynamic manipulation to keep mean blood pressure above 85 mm Hg during the first 5 days postinjury.	To assess the efficacy and timing of surgery; Modified Frankel score of Benzel and Larson as well as Yale Motor scale were used to compare patients on presentation and at follow-up, which was at 3,6 , 9 and 12 months post-injury
Cohn et al. (2010)	C spine only	17	Retrospective analysis of the charts of patients admitted to a single center with complete tetraplegia between 2000 and 2006. Neurological outcomes were examined in the patients with relation to their MAP during first 7 days post injury. MAP values and clinical results were collected from staff notes in ICU and laboratory computer systems for 7 days post admission. Patient MAP values were then recorded as number of minutes a patient spent in six different categories: below a MAP of 65, between 65-70, between 70-75, between 75-80 between 80-85 and above 85 mm of Hg. Percentage of time a patient spent in each MAP category was used as final variable.	Assess improvement in ASIA motor index compared to first post injury neurological exam in relation to MAP values. F/u duration was from admission to discharge; length of stay was on average 22 days
Martin et al. (2015)	C and T spine	105	Retrospective review of propectively-entered trauma database at a single level 1 trauma center, looking at all acute cervical and thoracic SCI between January 2007 and June 2009. Hospital	Functional outcome based on ASIA Motor score improvement during acute hospitalization only; Mean length of stay

			electronic medical record was searched for lowest and average MAP for each hour of initial 72 h of hospitalization. Mean MAP and total number of episodic relative hypotensive events were calculated. Theoretic MAP set points were created (>90, >85, >70, >65 mm Hg) to which data was compared. Patients were divided in quartiles based on number of relative hypotensive events. Severity of SCI and functional improvement were assessed using ASIA motor score.	was 18 +/- 13 days
Levi et al. (1993)	C spine only	50	Prospective study conducted over a 14 month period at a Shock and Trauma center, between January 1990 and February 1991, including all patients with cervical SCI and a hemodynamic profile were included. With discovery of neurological deficit, patients c-spines were immobilized with Gardner-wells tongs; operative spinal reduction was performed with persistent canal compromise despite closed reduction attempts. All patients were invasively monitored through arterial and Swan-Ganz pulmonary artery catheters. Hemodynamic profile was recorded immediately after placement of invasive lines. Goal MAP of above 90 mm of Hg was maintained with fluid and vasopressors. Neurological assessments (Frankel score, ASIA motor score and Yale motor score) were recorded and compared and percentage of change was calculated. Outcome analysis endpoints were either death or 6 weeks post-injury	Neurological assessments (Frankel score, ASIA motor score and Yale motor score) were recorded and compared and percentage of change was calculated. Outcome analysis endpoints were either death or 6 weeks post-injury
Readdy et al. (2015)	C-spine (Central Cord only)	34	Retrospecitve cohort analysis of patients with Acute traumatic central cord syndrome presenting to a single Level 1 trauma center from 2005-2011. Adult patients with SCI admitted to ICU who received vasopressors to meet MAP goals >85 mm Hg for greater than 24 hours were included. Outcomes determined based on improvement in neurological function, as indicated by ASIA grade from admission to discharge and/or death.	Improvement in ASIA grade from admission to discharge and/or death.
Inoue et al. (2014)	C,T and L spine (Although not specified; 76% of patients had SCI above T6; 24% below T6)	131	Observational retrospective cohort study in order to evaluate effects of vasopressors on all patient with SCI admitted to a level 1 trauma center from January 2005 to December 2011, using a Neurosurgery database. Patients selected were adults with SCI and neurological deficit with admission to ICU; they also had to have had vasopressors given for a minimum of 24h. Vasopressor usage and complications were obtain from the medical records. Improvement in	Complications of vasopressor usage; neurological outcomes in patients receiving vasopressors post-SCI, as assessed by change in ASIA score. Neurological improvement was only assessed in acute stage (during hospitalization)

			ASIA scores were evaluated to assess neurological outcomes.	
Kepler et al. (2015)	C,T and L	92	Retrospective review of a prospectively entered trauma database from a single regional SCI center. All patients admitted with an acute SCI between October 2006 and June 2009 who were treated with MAPs >85 in the ICU for at least 5 days were included. Patients were then stratified based on presence of preexisting HTN. Primary outcome measure was change in the ASIA motor score between admission and day 5.	Change in the ASIA motor score between admission and Day 5
Vale et al. (1997)	C and T spine	77	Prospective study looking at the effects of volume expansion and blood pressure management in 77 patients presenting with acute spinal cord injury and neurological deficits. All patients were managed by using Swan–Ganz and arterial blood pressure catheters and were treated with immobilization and fracture reduction as indicated. Intravenous fluids, colloid, and vasopressors were administered as necessary to maintain mean arterial blood pressure above 85 mm Hg.	ASIA grade of injury was used to assess improvement in neurological status. F/u exams were performed at 6, 12 and 18 months after injury. Mean duration of f/u was 17 months.

Abbreviations

MAP: Mean Arterial Pressure, ASCI: Acute Spinal Cord injury

Table 5: Summary of Human Data

Study	Complete vs Incomplete injury	Method of Map Manipulation	Duration of Map Manipulation	Outcome assessment
Hawryluk et al. (2015)	29 of 74 patients were complete;	Dopamine, phenylephrine, levophed	5 days	AIS score change at discharge compared to upon admission to ICU
Wolf et al. (1991)	34 patients were complete, 13 patients were incomplete and 5 were intact	Not mentioned	5 days	Change in Modified Frankel Scale and Yale Motor Score
Cohn et al. (2010)	All patients had complete tetraplegia	3 patients received vasopressors (dopamine, Phenyephrine)	7 days	Change in ASIA motor index
Martin et al. (2015)	Not specified; Mean admission AMS was 44.32 +/- 26.93	Vasopressors used in 70 of 105 patients; the kind of vasopressors were not specified	Not specified; only first 72 hours of MAP data was assessed	Change in AMS score during acute hospitalization
Levi et al. (1993)	39 patients had complete motor deficit;11 were incomplete	Dobutamine and dopamine were used as pressors, titrated to hemodynamic parameters. Choice of vasopressor was based on hemodynamic profile. Dopamine was used in 20 patients, and dopamine and dobutamine were used together in another 21 patients for a mean duration of 5.3 days.	7 days	Modified Frankel score, ASIA motor score and Yale motor score were used and the percentage of change was calculated by dividing the score difference by the initial gap of the score to intact state. A sensory score, proprioception and sphincter status were also recorded
Readdy et al. (2015)	8 patients were complete; 26 had incomplete injury	Dopamine and Phenylephrine; Dopamine to 91% of patients; Phenylephrine to 65%.	Mean of 4.2 days	Improvement in ASIA grade from admission to discharge and /or death
Inoue et al. (2014)	66 complete patients and 62 incomplete patients were analyzed	Dopamine in 79 patients (60%); 44 phenylephrine (37%); both in 5 patients (3%)	5 days	ASIA score improvement during acute hospitalization; complications of each vasopressor such as ventricular tachycardia, troponin elevation, atrial fibrillation, tachycardia and bradycardia.
Kepler et al. (2015)	27 patients had complete injury; 65 had incomplete injury	Vasopressors not specified	Minimum of 5 days; median of 6 days (range of 3-15)	Change in AMS during first 5 days in hospital

Vale et al. (1997)	10 patients had complete injury at cervical level; 21 patients had complete injury at thoracic level; 25 patients had incomplete injury at cervical level and 8 at thoracic level	Crystalloid, colloid and vasopressors when required. Dopamine was primary vasopressor used. Levophed was added if needed. 63% of c-spine injuries and 31% of t-spine injuries required vasopressors	7 days	Change in ASIA grade over 18 month period

Abbreviations

MAP: Mean Arterial Pressure, ASCI: Acute Spinal Cord injury

Table 6: Summary of Human Data

Study	Primary Outcome	Secondary Outcome	Biases/Shortcomings	Overall impression
Hawryluk et al. (2015)	3 patients experienced neurological worsening; 35 exhibited no changes in AIS grade; 23 improved one AIS grade and 13 improved more than one AIS grade.	In the first 7 days, 28.8% of measures were below 85 mm Hg; 24.9% of measures were below 85 mm Hg in the first 5 days; these values did not change when AIS grade A patients were excluded from analysis The group achieving > 1 AIS grade improvement had the highest MAP and lowest proportion of measures below 85 mm Hg at every examined time point whether or not grade A patients were included in analysis; MAP was higher in this group only for first 24-72 hours after ICU admission	Retrospective study; Insufficient long-term follow-up. The denoted time periods begin with admission to ICU and not from time of injury. No baseline bp measures or a timeline for when the bp was augmented. Bp augmentation took place for 5 days instead of the suggested 7. Patients achieving >1 AIS grade improvement stayed long in the ICU and in the hospital on average and had greater opportunity for neurological improvement. No causative relationship established by this study. No control group where MAPs not augmented. No long-term f/u	Useful study in showing relationship between high frequency MAP measures and extent of neurological improvement, however no causative relationship established.
Wolf et al. (1991)	Immediate traction and or induction of general anesthesia and muscle relaxation reduced the dislocation in 40 patients, but 12 needed prompt operative reduction as their injuries failed to reduce with 4 hours. Stabilization was indicated in all patients but 3 patients did not undergo surgery.	On discharge, 7 of 34 (20.4%) with complete injury changed neurological grades; one gained ability to walk. 8 of 13 patients with incomplete myelopathy improved (61.5%). No statistically significant difference between those undergoing acute or delayed surgery. 25 of 48 surviving patients had longer than 1 year f/u; all of incomplete patients improved and half had no residual myelopathy.	Only patients with C-spine injury. Not primarily meant for assessing effects of MAP on spinal cord injury; MAP data is sparse; no mention of how MAP was increased in patients requiring it. No control group where MAPs not monitored/augmented.	Although not meant to study effects of MAP, all of these spine injured patients were admitted to ICU and had their MAPs closely monitored; Rates of improvement after therapy no different from previously published literature, despite supposed optimal MAP management
Cohn et al. (2010)	Avg. motor score at admission 19.8, average motor score at discharge 24.4; average change in motor score 4.6 (+/- 3.8); Percent of time with a MAP of 65 mm Hg or lower was inversely correlated to motor score gains ($R= -0.533$, $p<0.05$); However, percent	In a hierarchical regression analysis, after accounting for injury severity, the percent time a patient spent at a MAP less than 65 mm Hg accounted for 47% of additional variability in motor score gains. The percent of time a patient spent at a MAP less than 70	Retrospective review; Only 17 patients. Only patients with C spine injury. Only patients with complete injury. Blood pressure was calculated from discrete points and not continuously monitored. Patient's average recovery was only 4.6 points, which does not necessarily reflect an actual change in functional ability. No long-term f/u.	Shows that hypotension in patients with complete injury can be detrimental to neurological recovery; does not help prove or disprove the notion that forced hypertension improves neurological outcome in this patient population

	time spent above MAP of 75 mm Hg and motor score change was not significant (R= -.265, p=0.304). R^2 of correlation between motor score change and percent time spent with MAP of 65 mm Hg or below was 0.28, and for MAP of 70 mm Hg was 0.26. As percent time a patient spent with MAP of 75 mm of Hg or above changed, the R^2 was not significant (R= 0.07)	mm Hg accounted for 30% of additional variability in motor score gains. At higher MAP values, the relationship decreased and was not significant for values of 75 mm Hg or greater		
Martin et al. (2015)	At 90 and 85 mm Hg set points, statistically significantly higher number of relative hypotensive episodes related to lower admission AMS; however, no related difference in the change in AMS during acute hospitalization. This difference was no longer statistically significant at lower theoretic MAP set points.	The need for vasopressors correlated with the number of hypotensive episodes and inversely related to admission AMS at all theoretic MAP goal set points, but was not correlated with the change in AMS during hospitalization	Single center, retrospective review. No long-term f/u, only acute hospitalization results reported. Did not look for pre-existing hypertension in patients. Only looked at the lowest MAP during a 1 h period, but not documented how long hypotensive episode lasted. No patients with lumbar/sacral injury.	Study which showed lower MAPs, more frequent hypotensive episodes and an increased need for vasopressors occurred in patients with more severe injuries. These factors did not affect change in AMS during hospitalization. Does not support supra-physiologic MAPs in this patient population.
Levi et al. (1993)	At 6 weeks, neurological function was improved by at least one grade in 20 patients (40%), 9 died (18%), 21 remained in same functional grade (42%)	Overall mean PVRI (182 dyne.s/cm^5.m^2) was less than normal range (200 to 300 dyne.s/cm^5.m^2), was less than normal value in 58% of patients. Half the patients had lower than normal SVRI values. Generally, the group of patients who did not receive inotropic agents had an initial significantly higher mean blood pressure (13%; $P < 0.01$)and a trend toward higher PVRI (234 dyne·s/cm^5·m^2 versus 197.5 in patients who received inotropic drugs). Non-survivors had an expected lower cardiac index and even deterioration on two successive	No control group; f/u data only extends up to 6 weeks post-injury. Patients with C-spine injury only. Most of the patients in the analysis had complete injury.	Analysis of hemodynamic measures did not differentiate between complete and incomplete lesions or between patients with functional improvement. No benefit shown to supra-physiologic MAPs, although this study does advocate for the safety of aggressive monitoring and hemodynamic intervention.

		days in their oxygen delivery and consumption.		
Readdy et al. (2015)	Improvement of at least 1 ASIA grade was observed in 19 patients (56%); the remaining 15 patients had same ASIA grade at admission and discharge. 2 patients died during course of treatment (6%).	68% of patients receiving dopamine had cardiogenic complications compared to 45% for phenylephrine (non-significant), except in patients over age of 55 where dopamine's complication rate was significantly higher. This age group also had higher complication rate for all vasopressors (90% in this age group).	Retrospective in nature. Only 34 patients; no comparison group, everyone received vasopressors and had an increase MAP. Main focus of paper is on vasopressor complications. No long-term f/u provided.	Improvement in neurological status was statistically non-significant; also shows that patients with age over 55 at higher risk of cardiogenic complications when treated with vasopressors.
Inoue et al. (2014)	Logistic regression analysis demonstrated that complications (e.g., ventricular tachycardia, tro-ponin elevation, atrial fibrillation, heart rate > 130 or < 50, etc.) due to vasopressors were independently associated with the overall usages of dopamine (odds ratio [OR] 8.97; p < 0.001) and phenylephrine (OR, 5.92; p = 0.004), age > 60 years old (OR, 5.16; p = 0.013), and complete SCI (OR, 3.23; p = 0.028)	There was no difference in neurological improvement with either dopamine (OR, 1.16; p = 0.788) or phenylephrine (OR 0.96; p = 0.940). Incomplete SCI (OR, 2.64; p = 0.019) and surgery < 24 h after SCI (OR, 4.25; p = 0.025) were independently associated with improved outcome. In summary, vasopressors are associated with increased complications in SCI patients	Retrospective; main focus was not neurological outcomes; exact measure of how much each group improved in ASIA score was not documented. Long-term f/u of neurological outcomes was not available.	This study does not specifically address whether increased MAP improves neurological outcome; shows that older patients have increased complication rates with vasopressor usage.
Kepler et al. (2015)	HTN was an independent predictor of poor outcome, as patients with HTN had an average decline in their AMS of 7.6, compared with an average decrease of only 0.6 in AMS without HTN (p=0.04). Patients with HTN and an average MAP greater than 85 mm Hg had a decrease in their AMS by 6.4 +/- 7.4 compared with a decrease of 10.5 +/- 18.9 for patients	Despite having target MAP of 85 mm Hg, only 52.6% of patients with HTN and 46.4% of patients without HTN had a mean MAP greater than 85 mm Hg for 5 days(p=0.50); Only statistically significant variable identified between groups was that HTN group was significantly older (70.0 versus 46.5; p=0.00001)	Retrospective review; Neurological recovery of both groups poorly documented; no long-term follow-up; only specific group with HTN targeted in this study. Both groups did had MAPs <85 mm Hg for more than half of the time despite MAP goals.	This paper does not give any conclusive evidence of any benefit to MAPS>85 mm Hg, as both groups showed average decrease in AMS after admission

	with HTN and an average MAP less than 85 mm Hg (p=0.60; non-significant trend)			
Vale et al.	Sixty percent of patients with complete cervical spinal cord injuries improved at least one Frankel or American Spinal Injury Association (ASIA) grade at the last follow-up review. Thirty percent regained the ability to walk and 20% had return of bladder function 1 year post-injury. Thirty-three percent of the patients with complete thoracic spinal cord injuries improved at least one Frankel or ASIA grade. Approximately 10% of the patients regained the ability to walk and had return of bladder function. At 12 month follow-up, 92% of patients demonstrated clinical improvement after sustaining incomplete cervical spinal cord injuries compared to their initial neurological status. Ninety-two percent regained the ability to walk and 88% regained bladder function. Eighty-eight percent of patients with incomplete thoracic spinal cord injuries demonstrated significant improvements in neurological function 1 year post-injury. Eighty-eight percent were able to walk and 63% had return of bladder function.	No statistically significant difference between the preoperative neurological examination and the selection for, or timing of, surgery in patients with cervical or thoracic spinal cord injuries in this series (cervical, $p < 0.125$; thoracic, $p < 0.587$). Similarly, stratification of neurological recovery at the 12-month follow up for cervical and thoracic spinal cord injuries revealed no statistically significant impact of the timing of surgery with respect to outcome (cervical, $p < 0.985$; thoracic, $p < 0.352$)	Small group of patients; No detailed documentation of adverse events related to vasopressor use	Study upon which current guidelines are based; well controlled and managed study, however it is almost 20 years old. Gives some idea of benefits of increased MAP, but does not address side effects of such therapy

Abbreviations

MAP: Mean Arterial Pressure, ASCI: Acute Spinal Cord injury

Discussion:

Acute spinal cord injury (ASCI) is often a devastating injury with significant repercussions on our health care system. The 2013 AANS guidelines (18) suggest 7 days of MAP directed treatment, targeting MAPS of over 85-90. The hypothesis behind hypertensive therapy in early ASCI is that raising the MAP will subsequently increase spinal cord blood flow and prevent or minimize progressive ischemia; the progressive ischemia after acute injury extends to the surrounding white matter, leading to additional axonal and neuronal necrosis (29). These guidelines are based on level III evidence, which is the best evidence available for this treatment strategy.

The goal of our review was to try and assess the validity of this treatment by looking at all of the clinical evidence available in the literature regarding neurological outcomes in patients who had undergone MAP directed therapy after an ASCI. We were hoping this review would help shed light on the duration of the therapy as well as which vasopressors were most useful in manipulating MAP in the post injury period.

For the purposes of this review, we looked at both retrospective and prospective studies in which patients had a documented manipulation of their MAP after an ASCI with a documented neurological outcome. As expected, a vast majority of the studies were retrospective in nature. However, we were able to find two prospective studies (6,7).

Positive Studies:

Hawryluk et al. (22) performed a retrospective analysis of patients with ASCI who were admitted to ICU for 5 days and had a targeted MAP of at least 85 mm Hg. They had 36 of 74 patients show improvement of one ASIA grade or more. Although they could not establish a causative relationship between increased MAP and neurological outcome in these patients, their data was suggestive that MAP may only relate to neurological outcome in first 2-3 days after injury. They also suggest that the duration of time below treatment threshold may be of greater relevance to neurological recovery; the group achieving > 1 AIS grade improvement had the highest MAP and lowest proportion of measures below 85 mm Hg at every examined time point whether or not grade A patients were included in analysis. The MAP was higher in this group only for first 24-72 hours after ICU admission.

The study by Wolf et al. (24) was primarily meant to assess the efficacy of timing of surgery in patients with bilateral facet dislocation in the cervical spine. However, all of the patients looked at had hemodynamic manipulation to keep mean blood pressure above 85 mm Hg during the first 5 days post-injury. No statistically significant difference between those undergoing acute or delayed surgery. On discharge, 7 of 34 (20.4%) with complete injury changed neurological grades; one gained ability to walk. 8 of 13 patients with incomplete myelopathy improved (61.5%). 25 of 48 surviving patients had longer than 1 year follow-up; all of incomplete patients improved and half had no residual myelopathy.

Levi et al. (7) looked prospectively at patients with cervical spine injury over a 14 month period. These patients had invasive hemodynamic monitoring and a target MAP of 90 for a 7 day period. When looking at both complete and incomplete injured patients together, neurological function was improved by at least one grade in 20 patients (40%), 9 died (18%), 21 remained in same functional grade (42%) at 6 week follow-up.

Vale et al. (6) performed a prospective study looking at the effects of volume expansion and blood pressure management in patients presenting with acute spinal cord injury and neurological deficits. All patients were managed by using Swan–Ganz and arterial blood pressure catheters and were treated with immobilization and fracture reduction as indicated. Intravenous fluids, colloid, and vasopressors were administered as necessary to maintain mean arterial blood pressure above 85 mm Hg for 7 days. 60% of patients with complete cervical spinal cord injuries improved at least one Frankel or American Spinal Injury Association (ASIA) grade at the last follow-up review. 33% of the patients with complete thoracic spinal cord injuries improved at least one Frankel or ASIA grade. At 12 month follow-up, 92% of patients demonstrated clinical improvement after sustaining incomplete cervical spinal cord injuries compared to their initial neurological status. 88% of patients with incomplete thoracic spinal cord injuries demonstrated significant improvements in neurological function 1 year post-injury.

Negative Studies:

Cohn et al. (23) performed a retrospective chart review of patients presenting with complete tetraplegia to a single center. Neurological outcomes were examined in the patients with relation to their MAP during first 7 days post injury; the percentage of time each patient spent at different MAP values was documented and used as the final variable. In this study, the average motor score at admission was 19.8 and average motor score at discharge 24.4. Percent of time with a MAP of 65 mm Hg or lower was inversely correlated to motor score gains (R= -0.533, $p<0.05$);

However, percent time spent above MAP of 75 mm Hg and motor score change was not significant (R= -.265, p=0.304).

Martin et al. (26) did a retrospective analysis of a prospectively collected database of acute cervical and thoracic injured patients. The Hospital electronic medical record was searched for lowest and average MAP for each hour of initial 72 h of hospitalization. Theoretic MAP set points were created (>90, >85, >70, >65 mm Hg) to which data was compared. At 90 and 85 mm Hg set points, statistically significantly higher number of relative hypotensive episodes related to lower admission ASIA motor score (AMS); however, there was no related difference in the change in AMS during acute hospitalization. This study did not support supraphysiologic MAPs in this patient population.

Readdy et al. (27) performed a retrospective cohort analysis of patients with acute traumatic central cord syndrome presenting to a single Level 1 trauma center. Adult patients with SCI admitted to ICU who received vasopressors to meet MAP goals >85 mm Hg for greater than 24 hours were included. Improvement of at least

1 ASIA grade was observed in 19 patients (56%); the remaining 15 patients had same ASIA grade at admission and discharge. Two patients died during course of treatment (6%). The improvement in neurological status was shown to be statistically non-significant.

Inoue et al. (25) performed an observational retrospective cohort study in order to evaluate effects of vasopressors on all patient with SCI admitted to a level 1 trauma center. There was no difference in neurological improvement with either dopamine (OR, 1.16; p = 0.788) or phenylephrine (OR 0.96; p = 0.940). Incomplete SCI (OR, 2.64; p = 0.019) and surgery < 24 h after SCI (OR, 4.25; p = 0.025) were independently associated with improved outcome. This study did not specifically address whether MAP guidelines are effective in improving outcome, but it did show increased risk and complications in older patients with vasopressor use.

Kepler et al. (28) performed a retrospective review of a prospectively entered trauma database from a single regional SCI center. All patients admitted with an acute SCI who were treated with MAPs >85 in the ICU for at least 5 days were included. Patients were then stratified based on presence of preexisting HTN. Patients with HTN and an average MAP greater than 85 mm Hg had a decrease in their AMS by 6.4 +/-7.4 compared with a decrease of 10.5 +/-18.9 for patients with HTN and an average MAP less than 85 mm Hg (p=0.60; non-significant trend). Despite having target MAP of 85 mm Hg, only 52.6% of patients with HTN and 46.4% of patients without HTN had a mean MAP greater than 85 mm Hg for 5 days. This paper does not give any conclusive evidence of any benefit to MAPS >85 mm Hg, as both groups showed average decrease in AMS after admission.

Balance of Evidence:

The evidence that we have compiled does not provide us with a clear answer to the question of whether there is benefit to supratherapeutic MAP in patients with ASCI. It does however highlight a few important points which should be taken into consideration when treating this type of patient in the acute phase.

Based on the data, it could be argued that the most important aspect of hemodynamic management in patients with ASCI is to keep them normotensive. Patients who were hypotensive uniformly did poorly. This data is in agreement with the data and outcomes in patients with traumatic brain injury. In animal models, pushing the MAP far above physiological levels increased spinal cord hemorrhages (14,15). This is unlikely to be of benefit in a clinical setting. Therefore the focus should be on maintaining normotension especially in the early period of injury.

Some of the data presented suggests that the first 2-3 days might be the most important period in ASCI for hemodynamic management. The original 7-day period of therapy was an arbitrarily chosen number. Many centers would be unwilling to keep an otherwise hemodynamically stable patient without any life threatening injuries in an ICU bed for 7 days. If the acute observation and treatment period were proven to be shorter, perhaps the burden on the system would be more acceptable.

The patients who are most likely to show improvement with any treatment are patients with incomplete spinal cord injuries. Careful thought should be given to starting patients who present with complete injuries on vasopressors and pushing

their MAP goals, especially in elderly patients who are at risk of cardiac and pulmonary complications (27).

In the studies that were looked at, little or no consideration is given to patients who present with lumbar injuries. It is therefore unclear whether these patients benefit from supraphysiologic MAPs in the acute period. Robust evidence in the form of a prospective study is required to definitively exclude any benefits of hypertensive therapy in the acute phase for this population of patients.

Conclusions:

Although no definitive conclusions could be reached based on the data collected, this study does give valuable insight into future avenues of research on the topic of hemodynamic management in ASCI as well provide guidelines for refinement of future study design. Specific questions such as benefits of hypertension, duration of MAP directed therapy, benefits in patients with complete injury and benefits in lower spinal injury need to be further studied in well designed prospective trials that conclusively document functional outcome and contain and a reasonable control group for comparison.

Performing consecutive literature reviews of both animal and human literature allowed us perspective on the short comings of both prospective and

retrospective data available on the subject of MAP directed therapy in ASCI. Using the data, we set out to design a prospective, randomized trial with the goal of answering specific questions regarding MAP in ASCI; for example, is a MAP goal of 85-90 mm of Hg a valid recommendation? Is this a valid recommendation for all groups of patients (C-T-L spine)? What is the ideal duration of MAP directed therapy? etc. Given the complexity of the question as well the difficulty implementing a large study in this population, we sought to design a simple study in order to possibly come to a definitive conclusion. This pilot study design is discussed in Chapter III.

Chapter III

Pilot Study Design

The Need to Determine Whether or not Mean Arterial Pressure (MAP) Directed Therapy Should be Instituted in Patients with Acute Spinal Cord Injury (ASCI):

The occurrence of hypotension has been shown to be associated with worse outcomes after traumatic injury, including severe head injury. A prospective controlled assessment of the effects of hypotension on acute spinal cord injury (ASCI) in humans has not been performed. Animal models of ASCI have been created in laboratory and data is extrapolated to the clinical setting, suggesting that hypotension contributes to secondary injury after ASCI by reducing spinal cord blood flow and perfusion. Hypotension in animal models of ASCI result in worse neurological outcome. This has been shown in at least two of the studies(10,11) which were assessed in our scoping review of the animal models of ASCI. Current AANS guidelines (18) claim that there is insufficient evidence to support treatment guidelines. The "options" given include maintaining a MAP of 85-90 for first 7 days following ASCI "to improve spinal cord perfusion". Only Class III evidence exists that a mean arterial pressure (MAP) directed therapy, goal 85 to 90 mm Hg, in patients with ASCI improves neurological outcome. This recommendation comes largely from a single pilot study conducted by Vale et al (6). Strong scientific evidence is lacking with respect to the actual target MAP that should be achieved in ASCI patients and length of time for target MAP post injury. Various reviews of this topic have been conducted over the past decade, which have arrived at the similar conclusion that strong clinical evidence is lacking. A recent systematic review by Casha and Christie in 2011 (31) has recommended a target MAP of at least 85 mm

Hg for up to 7 days post injury, based on weak evidence identified by a substandard systematic review design. Concerns have been raised around potential risks of maintaining a MAP of 85-90 mm Hg, with the primary concern being the aggressive use of vasopressors, particularly in elderly individuals with cervical SCI who are more prone to cardiopulmonary complications. Given the lack of conclusive evidence on the topic and that the potential risk associated with the proposed therapy, we decided to undertake a review of the animal models and human studies on the topic, as discussed in Chapters I and II.

Although we could not draw any definitive conclusions, we were able to highlight certain facets of previous studies that should potentially be modified for a future prospective study. For example, we highlighted in Chapter II that the period of 7 days was arbitrarily chosen, and that the data showed that perhaps the first 2-3 days post-injury were the most important for hemodynamic management. A shorter duration of MAP directed therapy would improve the practicality and feasibility of a prospective study.

We were also able to demonstrate that the animal studies in which the MAPs were pushed to supraphysiological levels showed a higher incidence in spinal cord hemorrhages. As a result it would be reasonable to eliminate a hypertensive group from a prospective study that would be undertaken.

In our review, we noticed that there were few studies that addressed MAP directed therapy in lumbar spine and cauda equina injuries. Given that below the conus medullaris the injury would be to peripheral nerves, it is unclear whether the

conclusions regarding MAP directed therapy in spinal cord injured patients can be extrapolated to this population. This should be addressed in a prospective study.

In our review of both the human and animal literature, we noticed that there was usually little to no improvement in patients who present to hospital with a complete (ASIA A) ASCI. If there is no meaningful recovery despite MAP directed therapy in this population, it would be useful to know. They can then be spared unnecessary medical management, which could be beneficial in an already hemodynamically unstable population.

The choice of vasopressor appears arbitrary and seems to depend on physician preference. It would be useful to know whether certain vasopressors are more beneficial in the setting of ASCI; this will help guide therapy and avoid unnecessary and unwanted complications.

We propose a Pilot Study to collect prospective data in our ASCI population, to assess if increased MAP goals (85-90 mm Hg) for a specified duration of 5 days will have any effect on neurological outcome, more specifically improvement in the patients ASIA grade of injury compared to initial presentation. As secondary outcomes, we will be looking at adverse effects of vasopressors, difference in improvement in complete vs. incomplete neurological injuries, and whether choice of vasopressor influences neurological outcome. The results of this trial will be vital in acquiring information to guide our management of ASCI patients, and whether the benefits of aggressive MAP goals and ICU admission outweigh the risks associated with vasopressor use. Vasopressors have been associated with cardiac strain, ischemic chest pain, tachycardia and in extreme cases cardiac failure and

death, particularly in at risk populations. The participants in this study will be exposed to the potential risks associated with vasopressor use, which will be explained to them in detail at time of consent.

The Proposed Trial:

We propose a double-blinded trial design to assess whether or not MAP directed therapy, with goal MAPs above 85-90mm of Hg, improve neurological outcomes in patients with ASCI. Improvement of ASIA score (compared to ASIA score on presentation) will serve as our primary outcome. As secondary outcomes we will be looking at adverse effects of vasopressors, difference in improvement in complete (ASIA A) vs. incomplete (ASIA B, C, D and E) neurological injuries, and whether choice of vasopressor influences neurological outcome. We propose to include all levels of spinal cord injury, cervical, thoracic and lumbar, who present to hospital in the acute stage with neurological deficits.

We propose our inclusion criteria to be all patients presenting to the Health Sciences Centre with ASCI and new neurological deficit who are 18 years and older and residents of Manitoba. Exclusion criteria will include age under 18, serious concomitant injury causing hypotension, traumatic brain injury or other injury which prevents accurate baseline dermatomal and myotomal exam, previous stroke or traumatic brain injury contributing to pre-existing neurological deficit and absolute contraindication to vasopressor use.

The population of patients with ASCI will be centrally randomized into intervention and control groups, using an online randomization service. The

intervention group will be admitted to ICU for a duration of 5 days, with the goal of measuring and maintaining MAP in these patients at or above 85 to 90 mm of Hg for as long possible during this 5 day period. Fluid as well as vasopressors will be primary means of maintaining the MAP at this level. The choice of vasopressor in cases where necessary will be left at the discretion of the Intensive Care Physician, and will be included in the secondary outcome analysis. The control group will also be admitted to ICU for the duration of 5 days; however the MAP will not be pushed in these patients. Vasopressors will only be used in these patients for the purpose of maintaining normotension (SBP >90 mm of Hg). Both of these groups will have continuous recording of MAP using Arterial lines. This data will enable us to determine what percentage of the time their MAPs were within the target range during the 5 day treatment period.

The treatment duration, as mentioned, will be 5 days. After obtaining baseline ASIA score as early as possible after the injury, we propose follow up neurological exams (determination of ASIA score) for the purpose of outcome measures at 5 days, 1 month, 3 months, 6 months and 12 months. This duration of follow up will enable full extent of neurological recovery as is commonly quoted in the literature, as well as tell us the extent of neurological recovery in the Acute and subacute phases of injury. The physicians performing all neurological exams will be blinded to treatment allocation.

We propose this trial be localized to a single location, at the Health Sciences center in Winnipeg. All of the ASCI patients admitted to Neurosurgery and Orthopedics are treated in this center. All patients will be admitted to the Surgical

ICU; in case of unavailability of beds, medical ICU will be used for admission of the patients in question. No collaboration with other centers is planned at this time.

Only one similar study has been conducted in a prospective fashion by Vale et al. (6) in 1997; however, this study did not have a control group to compare results. All 77 patients involved in the study were treated with aggressive management of MAPs. In this study, 88% of patients with incomplete injury showed neurologic improvement at the 12 month mark. We do not think there will be a substantial difference between the control and treatment groups, based on the retrospective data available in the literature (7,23,26). We therefore hypothesize that approximately 78% of patients in control group will show neurologic improvement at the 12 month mark. We used this difference to perform a power calculation. Assuming an Alpha of 5% and a Power of 80% for the study, we will require 398 patients per arm.

Although the Health Sciences Center is a large volume trauma center, recruiting almost 800 patients will be a long-term endeavor. With a combined average of 15-20 traumatic spine injuries on both the Orthopedic and Neurosurgery services per month, we estimate recruitment will take between 3.5 and 4 years to complete. Recruitment will be the responsibility mainly of the PI and authors mentioned above, namely Neil Berrington, Behzad Sabit and Fred Zeiler. The resident physicians and physician assistants on call will be educated about the trial and will aide in recruitement. The patients will be consented for the study with minimal delay after their arrival to hospital and entered into the database.

Given the single location as well our proximity to the associated rehabilitation center, we believe the loss to follow-up will be minimal. We anticipate minimal compliance issues, as the patients in question will all be residents of Manitoba in nearby rehabilitation facilities with routine follow-up exams scheduled with both rehabilitation physicians and their surgeons. The remote follow-up exams can be performed with the help of our associate Rehabilitation Physicians who will be blinded to treatment allocation.

We propose an intention to treat analysis, including all patients who were randomized to treatment or control groups. Data will be analyzed at each proposed follow-up interval, namely 5 days, 1 month, 3 months, 6 months and 12 months. We will perform a subgroup analysis of patients with complete neurological injury (ASIA A) to see whether they improve as readily as patients with incomplete neurological injury. The literature has shown that these patients do not show the same rates of improvement as patients with incomplete injuries. They will be included in our intention to treat analysis, however a separate analysis of the results will be conducted using only patients with ASIA B to E scores on presentation.

This study will help us take a large step towards clarifying appropriate guidelines for treatment of ASCI patients. If no benefit is shown with MAP directed therapy, it will potentially help us avoid the cost to the healthcare system associated with prolonged stays in intensive care units for patients who are otherwise stable with isolated spinal cord injuries. If a clear benefit is shown, it will help guide physicians towards more definitive management of patients, in a scenario where not all physicians agree on the utility of the therapy in question.

Trial Management:

The proposed trial will be managed and coordinated primarily by a dedicated research assistant from within the department of Neurosurgery at the HSC. She will be responsible for data entry as well as patient consent at time of recruitment. She will ensure appropriate follow-up and timing of follow-up. She will also enter patients into a central database for randomization.

Our research assistant will be advised and assisted in the day to day activity of the trial by the steering committee, which will also oversee other vital activities such as patient safety while enrolled in the trial. This steering committee will be composed of a Neurosurgeon, Orthopedic Spine surgeon, Rehabilitation Physician, Intensive Care Physician, Nursing coordinator from ICU as well as our Biostatistician. The members of this steering committee will not be involved in the data acquiring or patient management aspects of the trial and will serve in a purely administrative capacity.

The PI on the trial, Dr. Neil Berrington, as well as Drs. Sabit and Zeiler will be responsible for identification and recruitment of patients for the trial. They will also be involved in acquiring follow-up neurological exams, especially at the 5 day period. They will be blinded to patient allocation. The three above mentioned physicians will share the responsibility of authorship for the final write-up.

APPENDIX A:

List of Variables and their synonyms used

Var.1: Traumatic Spinal Cord injury	Var.2: Spinal Cord perfusion Pressure	Var. 3: Functional Outcome
Spinal Cord injury Spinal cord damage Traumatic injury spinal cord Spinal cord compression Spinal trauma Compression spinal cord Injured spinal cord Acute spinal cord injury Trauma spine Post-traumatic spinal cord injury Traumatic spine injury Trauma spinal cord Spinal cord	Perfusion therapy Hypertension therapy Hypotension Vasopressors Cord perfusion pressure MAP directed therapy Blood pressure directed therapy Blood pressure management Spinal cord perfusion Targeted MAP Hemodynamic Parameters Perfusion Perfusion pressure Hemodynamic Management	Functional Result Neurologic outcome Neurologic recovery Functional recovery

Example Search Strategy:

1. traumatic spinal cord injury.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

2. spinal cord injury.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

3. spinal cord damage.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

4. traumatic injury spinal cord.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

5. spinal cord compression.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

6. spinal trauma.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

7. compression spinal cord.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

8. injured spinal cord.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

9. acute spinal cord injury.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

10. trauma spine.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

11. post-traumatic spinal cord injury.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv,

kw, bt, id, cc, nm, kf, px, rx, an, ui]

12. traumatic spine injury.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

13. trauma spinal cord.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

14. spinal cord.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

15. remove duplicates from 1

16. remove duplicates from 3

17. remove duplicates from 4

18. remove duplicates from 6

19. remove duplicates from 7

20. remove duplicates from 8

21. remove duplicates from 9

22. remove duplicates from 10

23. remove duplicates from 11

24. remove duplicates from 12

25. remove duplicates from 13

26. 2 or 5 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. spinal cord perfusion pressure.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

28. perfusion therapy.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

29. remove duplicates from 27

30. remove duplicates from 28

31. hypertension therapy.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

32. hypotension.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

33. vasopressors.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

34. cord perfusion pressure.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

35. remove duplicates from 34

36. map directed therapy.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

37. blood pressure directed therapy.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

38. spinal cord perfusion.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

39. targeted map.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

40. remove duplicates from 38

41. remove duplicates from 39

42. perfusion.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

43. perfusion pressure.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

44. 29 or 30 or 31 or 32 or 33 or 35 or 36 or 37 or 40 or 41 or 42 or 43

45. functional outcome.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

46. functional result.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

47. neurologic outcome.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

48. neurologic recovery.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

49. functional recovery.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, bt, id, cc, nm, kf, px, rx, an, ui]

50. remove duplicates from 48

51. 45 or 46 or 47 or 49 or 50

52. 26 and 44 and 51

53. remove duplicates from 52

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