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Jayne Schroeder
University of New England

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Augmented Mean Arterial Blood Pressure and Vasopressor Selection in Patients with Spinal
Cord Injury.

Jayne Schroeder, SRNA

University of New England

Summer Semester 2019

Abstract

Blood pressure management in the acute period following spinal cord injury is a critical concern; one that anesthesia and critical care providers are often able to directly measure and regulate. It has been hypothesized that supraphysiologic blood pressure maintenance during this acute phase may improve recovery, however there is limited high-quality evidence to reinforce and guide management. Based on included prospective and retrospective studies, which provide the highest level of evidence available, The American Association of Neurologic Surgeons does provide the following level III recommendation: MAP goals of 85–90 mm Hg for 5–7 days post-injury should be considered. With regard to the optimal vasopressor, dopamine should be avoided. Norepinephrine should be considered as a first-line agent for cervical and upper thoracic spinal cord injuries, given evidence that it has a lower risk profile than dopamine. For injuries in the mid to lower thoracic spine, norepinephrine or phenylephrine should be considered as first-line agents. In summary, blood pressure management should not be overlooked and proper utilization could result in significant improvements in quality of life and hope for recovery.

Introduction

The management of spinal cord injuries (SCI) presents a unique set of challenges to anesthesiologists and is an area of ongoing research and best-practice development. One focus of ongoing research is the utilization of arterial catheters to measure and maintain blood pressure at supraphysiologic levels immediately post-injury to promote adequate end-tissue perfusion as well as the removal of accumulating cellular waste products at the site of injury. This technique

has shown benefit, though detailed interactions between vasopressor utilization and outcomes have thus far been difficult to identify due to the relatively low number of severe spinal cord injuries across the population (Kepler et al., 2015). As a result, strong recommendations by governing bodies have not been forthcoming. The American Association of Neurological Surgeons currently lists MAP maintenance $>90\text{mmHg}$ as a level III recommendation, indicating that this practice is supported by available data, though the evidence is lacking and future clinical research is indicated. The goal of this project is thus to review both historic and current literature to find cases of SCI where supraphysiologic MAP is beneficial in promoting enhanced recovery. A secondary goal of this literature review is to uncover anesthetic implications for blood pressure management of patients with SCI. Cardiovascular complications after spinal cord injury often necessitate the use of vasopressors for management and the ideal vasopressor for use in this population is controversial and often difficult to study. This paper aims to highlight the specific studies utilized for ongoing recommendations of MAP maintenance in patients with spinal cord injuries and also evaluate areas that supraphysiologic MAP therapy may not be indicated or provide limited clinical benefit. This paper will also elucidate several studies that evaluate the efficacy of select vasopressor agents, as there is data that suggests certain agents may provide improved outcomes.

Physiology of augmented MAP therapy

Multiple animal models and human studies dealing with neural tissue contribute to the hypothesized physiology supporting MAP therapy in SCI patients. Maintenance of elevated MAP goals seems to provide a neuroprotective effect via two unique pathways (Readdy, W.

Dall, S. 2016). The first is through mitigating episodes of hypotension commonly experienced in these patients. This hypotension can be systemic, as induced by neural trauma to sympathetic neurons that innervate the heart and blood vessels thus leading to erratic blood pressure control. Hypotension may also be highly localized to the level of trauma, as bony impingement of neurovascular bundles is often a component of traumatic spinal cord injuries. This often requires surgical decompression; though artificially elevated blood pressure may enhance blood flow even through neural vascular beds that might otherwise be compromised at unaltered blood pressures. This systemic and localized hypotension is further compounded by the frequent occurrence in many high level SCI patients of severe hemodynamic instability induced by neurogenic shock and autonomic dysreflexia.

The first goal of MAP therapy can thus be stated as maintaining adequate systemic perfusion and oxygen delivery to highly dependent neural tissue. Without this perfusion, hypoxia and inadequate nutrient delivery to the injured site can impair or even halt natural cellular function. The presence of hypoxia at the injury site can lead to rapid failure of the Krebs's cycle and impair neuronal maintenance of ATP levels with further damage occurring rapidly. The second goal of neuroprotection is the utilization of enhanced blood flow through neural-vascular beds to increase mobilization and clearance of waste products. By increasing cytokine and other inflammatory marker clearance it may be possible to limit excessive inflammatory damage and secondary injury to the spinal cord in the days and weeks following spinal cord injury. There currently exist multiple other intervention modalities directed at promoting cellular oxygen utilization and waste product clearance such as steroid therapy and periods of hypothermia that are outside of the scope of this paper.

Background

The concept of MAP resuscitation had previously been studied and shown to be efficacious in brain injury patients, but its utilization in SCI was not widely popularized until Vale et al. (1997) published an article evaluating combined medical and surgical treatment after acute spinal cord injury. The study hypothesized that tightly controlled blood pressure augmentation would aid in maintaining spinal cord blood flow and prevent some effects of secondary injury. The study design prospectively examined 64 SCI patients starting in 1992 with trauma ranging from C1-T12 who were treated with volume resuscitation and pharmacologic blood pressure augmentation to maintain supraphysiologic MAP goals > 85 mmHg for a minimum of 7 days post-injury. All patients started treatment within 36 hours of initial injury. There was no control group for this study, as severe SCI are a relatively rare occurrence and neurologic deficits and recovery vary widely between patients making direct comparison difficult. Outcomes were then compared to expected results on the basis of recovery experience in patients with SCI who had been managed without aggressive volume and blood pressure augmentation. All patients were managed in an ICU with Swan-Ganz and arterial blood pressure catheters for accuracy of results and precision management. Goal MAP was achieved with intravenous crystalloids, colloids, and vasopressors. Many of these patients also received decompression, stabilization, and fusion in select cases.

Results were stratified into complete SCI and incomplete SCI to differentiate between severity. As might be expected due to the traumatic nature of injury, neurologic recovery throughout the study group was variable and often incomplete; though this study did supply results that exceeded expected outcomes based on historic projections of SCI recovery. Results were reported in both American Spinal Injury Association (ASIA) grade (see table below for full results) and motor index score (MIS). Results indicate that incomplete SCI treated with MAP

goals resulted in clinical improvement for 92% of patients studied after 12 months. 60% of patients with complete cervical spinal cord injuries improved by at least one ASIA grade at 1 year follow up (see Appendix A for grade system). Please see table 1 for data pertaining to improvement of ASIA score from initial injury to 12 month follow-up. Of note, many of these patients continued to improve after this 12 month assessment and none lost neurologic function or increased their ASIA grade during the course of the study.

TABLE 1

*Outcome improvement in 64 patients with spinal cord injury according to ASIA Impairment Scale**

Initial ASIA Grade	No. of Patients	Outcome ASIA Grade at 12-Mo Follow Up				
		A	B	C	D	E
cervical cord injury						
A	10	4	1	2	3	—
B	6	—	1	1	4	—
C	8	—	—	1	4	3
D	11	—	—	—	6	5
thoracic cord injury						
A	21	14	2	3	2	—
B	5	—	1	2	2	—
C	1	—	—	—	1	—
D	2	—	—	—	—	2

*No patient had an initial ASIA grade of E. — = not applicable.

Legend: numbers represent patient n, letters represent ASIA grade at initial presentation (y axis) and at 12 month follow up (x axis)

In addition, the study did not show an increased instance of hypertensive hemorrhage, stroke, myocardial infarction, or death in the mean 17 month tracking period after patient injury (Subsequent studies evaluated with more sensitive measures of complications do show increased morbidity with vasopressor utilization). Based on the outcomes of the study, it was concluded by the ASIA that aggressive cardiopulmonary resuscitation efforts result in improved neurologic outcomes in patients with acute SCI. The results of Vale et al formed the basis for the 2012 Level III recommendation from the American Association of Neurologic Surgeons (AANS) regarding cardiopulmonary resuscitation in SCI. These guidelines state that hypotension should specifically be avoided and a goal MAP of 85-90mmhg should be targeted in the first 5-7 days after acute SCI. These guidelines have since formed the basis of care for many facilities despite the fact that subsequent studies have been unable to advance this level of recommendation. Authors of Vale et al. state that the ideal supraphysiologic MAP to maintain has yet to be established, and the ideal vasopressor for this application requires additional investigation.

Two other studies require brief mention as being fundamental articles establishing supraphysiologic MAP as a possible intervention for SCI management. Levi et al. (1993) performed a prospective study in which the authors described the outcomes of a group of 50 patients who underwent spinal immobilization or fixation as indicated, with their post-injury care at a trauma center between 1990 and 1991. A MAP goal higher than 90 mm Hg was maintained with fluids and dopamine for 7 days post injury. Some patients required the addition of dobutamine for additional support. 82% of patients showed stable or improved neurological

function at the 6-week follow-up as measured by their ASIA grade, and the authors concluded that pursuing aggressive MAP goals was feasible and of relatively low risk. Wolf et al. (1991) independently conducted a retrospective review of data for 52 patients who sustained a SCI between 1987 and 1990 due to bilateral facet dislocation. The patients were managed after decompression with an MAP goal greater than 85 mm Hg for 5 days. Twenty-two patients underwent follow-up for at least 12 months post-injury and all of these patients had stability or improvement in their functional grade. Neither of these last two studies included comparison groups, though they provided a foundation for subsequent investigation. In summary, these studies all point to the likelihood that increased MAP >85 supports long-term recovery, but none have the power to state it definitively.

Review of recent literature

Subsequent studies have continued to reinforce the hypothesis of earlier investigations: augmented MAP seems to improve long term outcomes. The papers included here will help to elucidate the subtleties of this hypothesis through unique populations and study designs.

Cohn et al. (2010) retrospectively reviewed 17 patients at Santa Clara medical center presenting with tetraplegia between 2000 and 2006. MAP recording was performed at least 3 times daily for 7 days postinjury. The authors estimated the amount of time patients spent with MAP above thresholds of 85, 75, and 65 mm Hg. The authors estimated that patients had MAP values greater than 85 mm Hg 33% of the time, greater than 75 mm Hg 65% of the time, and greater than 65 mm Hg 91% of the time. They also showed that the percent of time with a MAP of ≤ 70 mm Hg was inversely correlated to motor score gains. The correlation was insignificant

for time spent at a MAP of >75mm Hg, thus setting an upper limit of benefit achieved with MAP augmentation for the purpose of this study. Neurological outcome as measured by AIS grade and ASIA motor score was not found to be related to duration of time at a goal of MAP greater than 75 or 85 mm Hg. This study importantly displays that there seems to be no benefit for maintaining MAP at values greater than 75, though it does not reveal what deleterious effects hypotension may have.

Hawryluk et al. (2015) retrospectively reviewed MAP data for 74 SCI patients who underwent post-injury treatment between 2005 and 2011 at San Francisco General Hospital and were managed with a MAP goal greater than 85 mm Hg for 5 days post injury. All patients were managed with arterial catheters and data was collected automatically every 1 minute during their intensive care stay. The relationship between these values as well as the proportion of MAP recordings below 85mmHg was studied. The authors found that about 25% of all MAP's for the first 5 days post injury were lower than the goal. The patients who exhibited the greatest neurological improvement as measured by AIS grade had fewer MAP measurements lower than the goal compared with patients without neurological improvement. Thus this study displays that for their population roughly 1/4th of MAP values were lower than 85mmHg and that patients who displayed greater recovery had fewer episodes of hypotension. While this does not give concrete hypotensive values to avoid, it does provide evidence that hypotension may be associated with poor prognosis.

The authors reported that their data suggests that a MAP of 70–75 mmHg appeared to be the threshold at which neurological benefit is correlated with MAP goals. In addition, the authors noted that the first 2–3 days after injury with elevated MAP correlated most strongly with recovery. This correlation between MAP and eventual recovery decreased in strength over the

first week post-injury. Despite these findings, there is still not enough evidence to prove a causal relationship between recovery and blood pressure management, though a strong correlation does exist. The study does support that duration of hypotension may be more important than average MAP. Another important finding from the study is the correlation that MAP thresholds >85 are associated with higher degrees of neurological recovery.

Inoue et al. (2014) retrospectively reviewed 131 patients who were admitted with SCI between 2005 and 2011 at a level 1 trauma center and received vasopressors to maintain MAP goals of higher than 85 mmHg. Although this was a retrospective review, the MAP data were collected prospectively. This patient population was also analyzed in the studies by Hawryluk et al. and Catapano et al., which are also reviewed in this paper. MAP goals were maintained for 5 days before being relaxed to lower levels. AIS grades were collected as outcome measures up until the time of discharge from the hospital; no association was found between neurological outcome and the use of vasopressors to maintain MAP goals. There was no comparison or control group. Thus this study is equivocal in its findings and does not show any link between MAP goals and recovery.

Catapano et al. (2016) retrospectively reviewed 62 patients who presented between 2005 and 2011 at San Francisco General Hospital with traumatic SCI. Of note, this patient population was also previously studied by Inoue et al as well as by Hawryluk et al., both of which are summarized above. This further highlights the difficulty of finding even moderately sized novel study groups for human study of SCI. The authors compared the average MAP as well as the proportion of MAP lower than 85 mm Hg with their outcomes, as measured by comparing AIS grades at presentation and discharge. MAP was analyzed only for the first 3 days after injury.

There was a correlation between improvement and a greater proportion of MAP higher than 85 mm Hg in patients presenting with AIS Grade A, B, or C. This study thus flushed out two new points: that augmented blood pressure within just the first 3 days significantly correlated BP and neurologic improvement (thus seeming to indicate with no upper limit that higher MAP is better) and also that patients who initially presented with an AIS grade of D (see appendix A) did not display any change in neurologic improvement with augmented MAP. This may be because these patients with less severe spinal trauma are much less likely to have periods of hypotension.

Dakson et al. (2017) retrospectively reviewed 94 patients (after excluding 6 deaths and 64 cases of inappropriately coded SCI patients) who presented with SCI at an acute trauma center in Halifax Nova Scotia between 2006 and 2010. Their study sought to evaluate MAP management and timing of surgical decompression, thus providing an interesting set of data with two variables.

They found remarkably strong data that patients with a MAP <85mm Hg for at least 2 consecutive hours during the 5 day period postinjury were 11 times less likely to have an improvement in their American Spinal Injury Association (ASIA) grade when compared with patients whose MAP was ≥ 85 mm Hg ($p=0.006$). This association was found to be independent of early surgery or the severity of SCI. That said, at a mean of 252 days post-injury, a significantly greater proportion of SCI patients treated with early surgical decompression (< 24 hours) had some degree of neurologic improvement ($P=0.031$). Serial hourly MAP were collected for 50 of these patients. MAP lower than 85 mm Hg for more than 2 consecutive hours in the 5 days post injury was defined as suboptimal BP management. Finally their group also found that MAP treatment for 7 days as opposed to previous recommendations of 5-7 was associated with

improved outcomes and as such their facility adopted a protocol that called for maintenance of MAP \geq 85 mm Hg for 7 days post-injury.

In summary, maintenance of mean arterial blood pressure between 85 and 90mm Hg for the first 7 days following an acute spinal cord injury is almost universally recommended, though one studies show no benefit with maintaining MAP >75 (Hawryluk et al, 2015). That said, another study (Dakson et al, 2017) showed that MAP values <85 mmHg for >2 hours were associated with poor outcomes. Future studies may show that these values are actually complementary and represent relative upper and lower limits of blood pressure control. Subsequent studies will need to tease out the variability seen between these and other studies. Research is ongoing in this field and the recommendations of the American Association of Neurologic Surgeons continue to evolve as further research displays the areas where supraphysiologic MAP can provide the greatest benefit.

Spinal cord damage and vasopressor utilization in animal studies

Animal models offer a unique way to study SCI and interventions that would be otherwise impossible in human subjects for technical or ethical considerations. In regards to spinal cord damage, there have been many animal studies that contribute to our knowledge base. For this reason most of the existing knowledge regarding SCI pathology and potential interventions are derived from animal studies. A review of over 2200 articles (Sharif-Alhoseini et al, 2017) provides a wealth of data about the kinds of research that has been done in this field. They showed that the most common spinal region studied was thoracic (1790 articles, 81%) followed by cervical (265 articles, 12%), Lumbar (113 articles, 51%), sacral (16 articles, .07%),

unknown (64 articles, 2.9%), and other (16 articles, .7%). Their review showed that most studies were classified as mechanical traumatic injury (94.5%) as opposed to non-mechanical injury (5.5%) and also that the mostly widely studied species were rodents (92%). This review is significant to the research topic of MAP control as it highlights how few studies are performed in animals to evaluate the impact of MAP control following SCI. Of all included studies, only 61 (2.8%) included any sort of cardiovascular evaluation. One reason for this is that rodents represent a poor model for arterial blood pressure monitoring based on their small size. Another reason that few animal models have evaluated MAP control is the overall low number of studies evaluating cervical cord injury, as this is the group most likely to benefit from tight blood pressure control. Nevertheless, there are several animal studies that have significantly contributed to this area of investigation.

One such animal study, published in June 2018 after the above review, evaluates the comparison between norepinephrine (NE) and phenylephrine (PE) for augmenting spinal cord perfusion in a porcine model of spinal cord injury (Streijger et al., 2018). This article highlights the pharmacologic properties and potentially different effects these medications have on spinal cord blood flow (SCBF), oxygenation (P02), and downstream metabolites after injury. The model selected was a thoracic spinal cord contusion/compression at T10 with measurement of the spinal cord adjacent to the injury with a microdialysis probe inserted into the spinal cord to measure intraparenchymal SCBF, P02, hydrostatic pressure, and metabolism. Two sites were used for measurement including a proximal site 2mm from the lesion and a distal site 22mm from the lesion. The pigs were randomized to receive either NE or PE for MAP elevations of 20mmHg, or no MAP augmentation. Of note, neither NE nor PE showed significant improvement in SCBF during cord compression. Following decompression however, NE

resulted in slightly increased SCBF and P02, whereas decreased levels were observed for PE. Both NE and PE were associated with a gradual decrease in the lactate to pyruvate ratio after decompression. This study also revealed that PE was associated with greater hemorrhage through the injury site than in control animals. This study points to utilization of NE over PE for promotion of blood flow and oxygenation thus providing a physiologic rationale for the selection of a vasopressor in this population. Unfortunately there still exists a gap between human and animal models and applying this data to human patients requires a leap of inference.

Vasopressor selection in human models

Given that hypotension is strongly correlated with poor outcomes in SCI patients it follows that vasopressor management would be an important inclusion in care for these patients. Selection of vasopressors is often subject to particulars of the patient condition and is generally continued from emergency management. Data on selection of vasopressor for best efficacy in cases of spinal cord injury is lacking and difficult to collect. Human studies are lacking in terms of randomized control trials, but there are studies selectively comparing unique vasopressors to achieve specific MAP goals. One such study by Altaf et al. (2016) looked at the differential effects of norepinephrine (NE) and dopamine (DP) on cerebrospinal fluid pressure and spinal cord perfusion pressure (SCPP) after acute human spinal cord injury. 11 patients over the age of 17 with cervical or thoracic injury were enrolled in the study. NE and DP were evaluated in a crossover procedure to directly compare their effect on intrathecal pressure (ITP). ITP, MAP, and heart rate were continuously monitored in an intensive care unit where the study took place. SCPP was calculated as the difference between MAP and ITP. Results showed no difference in

MAP between NE and DP (84mmHg for both; P.033), though ITP was significantly lower with the use of NE (17 mmHg vs 20 mmHg DP, P<.001). This resulted in a net increase SCPP during NE infusion when compared to DP infusions (67 mmHg vs 65mmHg, P=.0049). These results seem to indicate that NE provides a more favorable environment for neural recovery as opposed to DP.

Another study that highlights the unique differences among available vasopressors is a 2015 study by Readdy et al. titled complications and outcomes of vasopressor usage in acute traumatic central cord syndrome (ATCCS). This retrospective cohort analysis looked at 34 patients with ATCCS who received vasopressors to maintain blood pressure at a single level 1 trauma center. Dopamine (DP) and phenylephrine (PE) were utilized and analyzed for complications during treatment. Results showed that DP was the most commonly utilized primary vasopressor (91%) with PE being used in 65% of patients. Vasopressors were administered to a goal of 85 MAP for a mean of 101 hours and notably all patients improved by a median of 1 ASIA grade regardless of vasopressor utilized. There was however no observed relationship between the timing of surgical intervention and complication rate. Cardiogenic complications associated with vasopressor usage were noted in 68% of patients who received dopamine and 46% of patients who received phenylephrine (P=.105). These complications included atrial fibrillation (5 in DP group, 0 in PE group), Tachycardia (9 in DP group, 3 in PE group), Bradycardia (4 in DP group, 7 in PE group), and ventricular tachycardia (3 in DP group, 0 in PE group). Please see table 4 below for complications. Of note, over 50% of these patients experienced some sort of cardiovascular complication, highlighting the fact that blood pressure augmentation is not a benign intervention.

TABLE 4.

Specific complication rates by individual vasopressor

Complication	No. of Patients (%) [*]	
	Dopamine	Phenylephrine
Patients w/ complications	21 (67.74)	10 (45.45)
Patients w/ multiple complications	2 (6.45)	1 (4.54)
Atrial fibrillation	5 (16.13)	0 (0)
Tachycardia (HR >130 bpm)	9 (29.03)	3 (13.64)
Bradycardia (HR<50bpm)	4 (12.90)	7 (31.82)
Ventricular tachycardia	3 (9.68)	0 (0)
Troponin levels	2 (6.45)	1 (4.54)

HR = heart rate.

*Percentages are based on the number of patients per category.

Legend- number and percentages(%) of patients experiencing complications with dopamine vs phenylephrine

Of note, patents over the age of 55 did show statistically significant increases in the complication rates when DP was used when compared with PE. This study thus potentially supports the restriction of DP to patients less then 55 years of age. The low N number and retrospective nature of this study do limit the findings significantly and prevent several conclusions from reaching statistical significance. That said, it is still clear from the results and table 4 that vasopressor selection directly impacts complications rates and that the unique profiles of commercially available agents should be considered before utilizing a particular vasopressor.

Potential risk with hypertensive therapy and vasopressor utilization.

This last study and associated table (#4) highlights some of the risks and potential complications from vasopressor use. A review by Inoue et al. (2014) evaluated the complications associated with vasopressor administration for the support of MAP goals in a cohort of 131 SCI patients. In this review, dopamine was found to be the most commonly utilized vasopressor (48%) followed by phenylephrine (45%), norepinephrine (5%), epinephrine (1.5%), and vasopressin (.5%). Logistic regression analysis demonstrated that complications due to vasopressors were independently associated with the overall usage of dopamine and phenylephrine, age >60, and complete SCI. The review found no difference in neurological improvement with either dopamine or phenylephrine when compared to one another. What the study did find to be associated with improved outcome was surgery <24 hours after SCI, or an incomplete SCI as the initial injury. This study does not have the power to show that vasopressors are associated with worse outcomes, but it does correlate vasopressor use with increased complication rates that might mitigate the potential benefit of their use. Results actually demonstrated high rates of vasopressor-induced complications, with 70% of patients experiencing an associated complication including tachycardia, (heart rate >130), bradycardia (heart rate < 50), ventricular tachycardia, elevated troponins, new onset atrial fibrillation, atrial flutter, skin necrosis, electrocardiogram (ECG) changes, ST changes consistent with ischemia, and acidosis (pH <7.0). These clinical findings should bring pause to the clinical decision to utilize vasopressors for hypertensive therapy and likely contribute to increased length of stay and patient hemodynamic instability. Future studies would need to incorporate new parameters including length of stay and morbidity analysis to more completely elucidate the side effects of vasopressor use in this patient population.

Another study calling into question the efficacy of vasopressors to maintain arbitrarily set values is a review article by Martin et al. (2015). Their group hypothesized that increased MAP goals and episodes of relative hypotension do not affect hospital outcomes. Their group theorized that poor outcomes are a byproducts of SCI severity and are independent of MAP maintenance. The findings seem to support their suspicion. Of note, this is the largest published cohort of acute SCI patients and evaluation of functional outcomes as it relates to set MAP goals during hospitalization giving it added quantitative power when compared to other studies. 105 cervical and thoracic SCI patients treated at a level one trauma and regional SCI center over a 2.5 year period were retrospectively reviewed with the lowest and average hourly MAP recorded for the first 72 hours of hospitalization. The authors used the American Spinal Injury Associations Motor Score (AMS) to determine severity of injury. AMS is a more complex scoring system than the ASIA as it allows for each limb to be scored separately instead of upper vs lower extremities. AMS is calculated by assessing function in 5 key muscle groups per extremity, and each muscle group has a maximum score of 5, creating a maximum score of 100. They found that at higher theoretic MAP set points (85 and 90) there were increased numbers of relative hypotensive episodes and lower ASIA scores, and therefore an increased need for vasopressors ($P=0.03$). They did not however show a statistical change in AMS by hospital discharge that matched with patients receiving vasopressors. Instead the need for vasopressors correlated with the number of hypotensive episodes and was inversely related to admission AMS.

They concluded based on this data that the frequency of relative hypotension and the need for vasopressors was related to severity of SCI and not the independent use of vasopressors. These episodes of hypotension and need for vasopressors did not affect the change in AMS during the acute hospitalization.

Readdy et al. (2016) also casts doubt on the reliance of mean arterial pressure goals to improve outcomes following penetrating spinal cord injury. While this is a technically unique subgroup of patients (penetrating trauma only), it does show that hypertensive management may not be appropriate in all cases of spinal cord injury. This study was performed at the brain and spinal injury center through the university of California, San Francisco, and included 14 patients with complete penetrating SCI's with an admission grade A (no motor or sensory function below level of injury) American Spinal Injury Association injury admitted from 2005-2011. This small cohort was compared to a group of 22 SCI patients involving blunt mechanism of injury. Both groups had complete injuries as indicated by ASIA grade of A (See appendix A). The two groups were compared in terms of neurological recovery, complications, interventions, and vasopressor administration. All patients received hypertensive therapy with vasopressors for an average time of 101.07 hours (± 34.96) hours.

Of the 14 penetrating injury patients, only 1 experienced any neurological recovery as determined by improvement in the American spinal injury association grade. Additionally, 71.43% of these patients with penetrating injuries experienced cardiogenic complications that may negate any benefit of hypertensive therapy. For comparison, in the blunt injury group there was improvement based on ASIA score in 8 of 22 patients. The study concludes that penetrating trauma may be a unique subgroup that is unlikely to benefit from supraphysiologic MAP therapy due to the more damaging nature of the injury and that more studies will have to be performed to provide a larger N number for study.

Another area of potential concern is the use of augmented MAP therapy in patients who are already hypertensive (HTN) at baseline. Kepler et al. (2015) conducted a retrospective case-controlled trial where he highlights that chronic HTN is an independent risk factor for poor

neurologic recovery. In this study, the authors highlight the autoregulatory physiology of blood flow to various organs and speculate that goal MAP of 85-90 may be inadequate for enhanced perfusion in these patients. 92 patients were gathered from a single regional SCI center between 2006 and 2009 that underwent HTN therapy in the intensive care unit for a minimum of 5 days. Patients were then stratified based on the presence of preexisting HTN. Statistically significant differences were evaluated by conducting inferential statistical analysis using chi-Square test or Fisher's test for categorical variable comparisons and the student's t-test. Of the 92 patients included only 22 met criteria for history of HTN. All patients had a target MAP >85, though only 52.6% of the patients with HTN and 46.4% of the patients without HTN had a mean MAP > 85 for 5 complete days post-injury. No difference in mechanism of injury ($P=.09$), level of spinal injury ($P=.76$), gender ($P=.1$), injury severity score ($P=.1$), number of patients undergoing surgery ($P=.07$), number of patients with a complete SCI ($P=.3$) was identifiable between the two cohorts. The only statistically different variable identified between the two groups was the HTN group was significantly older than the non-HTN group (mean of 70 years old vs. 46.5 years old respectively). HTN was an independent predictor of poor outcome as patients with HTN had an average decline in the AMS of 7.6 (100 represents full function). Patients with HTN with an average MAP that was greater than 85 mm Hg did show a non-statistically significant decrease in the AMS by 6.4, compared to a decrease of 10.5 for chronic HTN patients with average MAP <85. While the study numbers are too small to have predictive power, it does support the hypothesis that higher MAP may need to be utilized for patients with baseline hypertension.

Discussion

MAP augmentation in SCI patients in the acute post-injury phase has held significant interest for the past several decades, but there is still limited and low-quality evidence regarding the risks and benefits of this practice. The basis of MAP goals and duration are most commonly attributed to the study from Vale et al. (1997), which was evaluated above as prospective studies reporting the goal of elevation of MAP for a specified duration of time post-injury. Elevated MAP goals are still widely practiced based on a theoretical physiology, other retrospective reviews, case series, and anecdotal reports. MAP augmentation is also formally recommended by the AANS/CNS Joint Committee guidelines and will likely continue as a standard of care, though certain populations may eventually be excluded from the recommendation.

There are risks associated with establishing elevated MAP in the period after SCI, which include complications due to vasopressor use, invasive monitoring, decreased patient mobilization, and prolonged hospitalization (Inoue et al, 2014). Some of these risks, in particular vasopressor use, have been discussed above and display the potential to cause major complications. Current research is then directed at assessing the risk-benefit profile for vasopressors, given the lack of definitive high-level evidence of BP augmentation in improving neurological recovery after SCI.

With regard to the optimal MAP, there have been no direct comparison studies uncovered by this review that show differences in outcome with different MAP goals. The formal recommendation of MAP of 85–90 mm Hg appears to be derived from Vale et al. (1997) in which MAP goals of 85-90 mm Hg were chosen somewhat arbitrarily. There is the possibility that lower MAP goals may achieve similar results with less risk. Given that BP augmentation is currently the standard of care after SCI based on current recommendations, future studies in this

patient population involving control groups will have to carefully consider the potential ethical questions of providing nonstandard-of-care treatment to a control group.

There is currently a trial investigation that aims to answer the above question: Mean Arterial Pressure in Spinal Cord Injury (MAPS) trial: Determination of Non-inferiority of a Mean Arterial Pressure Goal of 65 mm Hg Compared with a Mean Arterial Pressure Goal of 85 mm Hg in Acute Human Traumatic Spinal Cord Injury (clinicaltrials.gov no. NCT02232165). This study is ongoing at the University of Texas Health Science Center in San Antonio and the University of Calgary in Alberta. Result from this study may reinforce or alter the AANS/CNS joint commission guidelines.

The duration of maintaining elevated MAP is currently recommended at 7 days, although no studies have compared different durations. A number of retrospective articles included here have reported pursuing elevated MAP goals for a total of 5 days and did not indicate adverse outcomes related to this duration. This may also change guidelines with future studies.

Recommended vasopressors for BP augmentation in SCI patients have varied but seem to favor phenylephrine for middle to low thoracic injuries and dopamine for high thoracic and cervical injuries, given its alpha and beta adrenergic effect (Strejiger et al, 2018). Norepinephrine has been used in recent studies, but its use over dopamine seems to be facility specific. Several studies here indicate that norepinephrine is superior to dopamine in the treatment of spinal shock, and that recommendation is backed by the AANS in their official recommendations (Readdy, W. Dhall, S. 2016).

ASIA grade of D (complete sensory function, partial motor function below level of injury) was not associated with improvement in one study (Catapano et al, 2016) and further study may show that these less severe injuries do not require supraphysiologic MAP.

Readdy and Dhall wrote an excellent review in *Neural Regeneration Research* (2016) titled *Vasopressor administration in spinal cord injury: Should we apply a universal standard to all injury patterns?* In it they review many of the above studies and emphasize that SCI is often treated as a homogenous injury pattern, despite the wide variations in injury and outcomes. Level of injury, mechanism of injury, presence of hemorrhagic spinal cord trauma, and pattern of intraspinal injury can all influence the results and may need to be considered independently to MAP. The advocate for clinical decision-making and judicious use of augmented MAP in some cases.

Limitations

This review of articles pertaining to supraphysiologic MAP maintenance and neurologic recovery in SCI patients is significantly limited by a number of important factors. At the individual study level, there were often low numbers of patients, follow-up was often limited, and almost all of the studies lacked comparison groups. These limitations are particularly relevant when studying neural regeneration as improvements in function can still occur years after the initial injury. Across each study, there were variations in MAP goals and outcome measures, and protocols differed significantly. At the review level, there exists the potential that this search did not uncover all relevant research, specifically articles not published in English.

Additionally there is significant possibility of reporting bias and the potential for not reporting all significant published information, as this literature review was conducted by one researcher. A complete review would require peer review and additional search criteria spanning non-English databases.

Conclusions

BP management in the acute period following SCI is an intervention of significant importance given the severe morbidity associated with SCI. Unfortunately, there is limited high-quality evidence to guide BP management, and further research is essential. Based on included prospective and retrospective studies, which provide the highest level of evidence available, The AANS does provide the following level III recommendation: MAP goals of 85–90 mm Hg for 5–7 days post injury should be considered. With regard to the optimal vasopressor, dopamine should be avoided. Norepinephrine should be considered as a first-line agent for cervical and upper thoracic SCIs, given evidence that it has a lower risk profile than dopamine. For SCIs in the mid- to lower thoracic spine, norepinephrine or phenylephrine should be considered as first-line agents.

Blood pressure management is just one of a multitude of interventions in the acute phase of injury, but it's importance as even a minor contributor to overall recovery should not be overlooked as the function preserved for future patients could result in significant improvements in quality of life and hope for recovery.

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ASIA Impairment Scale

A	Complete	No sensory or motor function is preserved in sacral segments S4-S5
B	Incomplete	Sensory, but not motor, function is preserved below the neurologic level and extends through sacral segments S4-S5
C	Incomplete	Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have muscle grade less than 3
D	Incomplete	Motor function is preserved below the neurologic level, and most key muscles below the neurologic level have muscle grade greater than or equal to 3
E	Normal	Sensory and motor functions are normal

Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply