

Percutaneous cervical sympathetic block to treat cerebral vasospasm and delayed cerebral ischemia: a review of the evidence

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ABSTRACT

Delayed cerebral ischemia (DCI) affects 30% of patients following aneurysmal subarachnoid hemorrhage (aSAH) and is a major driver of morbidity, mortality, and intensive care unit length of stay for these patients. DCI is strongly associated with cerebral arterial vasospasm, reduced cerebral blood flow and cerebral infarction. The current standard treatment with intravenous or intra-arterial calcium channel antagonist and balloon angioplasty or stent has limited efficacy. A simple treatment such as a cervical sympathetic block (CSB) may be an effective therapy but is not routinely performed to treat vasospasm/DCI. CSB consists of injecting local anesthetic at the level of the cervical sympathetic trunk, which temporarily blocks the innervation of the cerebral arteries to cause arterial vasodilatation. CSB is a local, minimally invasive, low cost and safe technique that can be performed at the bedside and may offer significant advantages as complementary treatment in combination with more conventional neurointerventional surgery interventions. We reviewed the literature that describes CSB for vasospasm/DCI prevention or treatment in humans after aSAH. The studies outlined in this review show promising results for a CSB as a treatment for vasospasm/DCI. Further research is required to standardize the technique, to explore how to integrate a CSB with conventional neurointerventional surgery treatments of vasospasm and DCI, and to study its long-term effect on neurological outcomes.

BACKGROUND

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe disease that affects six to nine per 100 000 people per year and results in significant morbidity and mortality.¹ Brain injury at the time of aneurysm rupture is a significant cause of these poor outcomes, but cerebral artery vasospasm and delayed cerebral ischemia (DCI) are a more insidious cause of neurologic injury, disability, and death. DCI is defined as the sustained neurologic deterioration that is not secondary to hydrocephalus, infection, or metabolic disarray.² Vasospasm and DCI occur 3–14 days following aSAH, and the pathophysiologic basis of vasospasm and DCI are multifactorial and incompletely understood. It is likely that impaired cerebral perfusion secondary to arterial vasospasm, microvascular thrombosis, and cortical spreading depolarization result in significantly reduced cerebral perfusion.³ If cerebral perfusion is reduced

significantly, cerebral infarction may occur, which may lead to permanent neurologic deficits and even death. Therefore, significant efforts are harnessed to identify patients at an increased risk of vasospasm and DCI.

Between 50% and 67% of patients with aSAH develop large cerebral artery vasospasm,⁴ but more than half of patients with arterial vasospasm do not develop neurologic symptoms. It is likely that these asymptomatic patients sustain sufficient cerebral perfusion to preserve neurologic function, whereas symptomatic patients with DCI likely suffer from more significant reductions in cerebral perfusion. Interestingly, studies have shown that endovascular and pharmacological treatment of large artery vasospasm have only a marginal impact on improving long-term neurological outcomes,^{5,6} which indicates that vasospasm is likely not the predominant cause of DCI.⁷ In support of this notion, the pattern of cerebral infarction due to DCI is often diffuse and frequently localizes to regions without proximal artery vasospasm.⁸

Limits of current treatments for vasospasm and DCI

Therapies for the treatment of vasospasm and DCI include medical and endovascular interventions. Medical therapy currently consists of permissive hypertensive therapy and administration of calcium channel antagonists.⁹ Oral nimodipine is the only class I, level of evidence grade A, therapeutic agent recommended by the American Heart Association/American Stroke Association for prophylactic treatment after subarachnoid hemorrhage. Permissive hypertension is another commonly performed therapy that carries a class I, level of evidence grade B recommendation.¹⁰ Nimodipine has a very modest effect on the development of arterial vasospasm, but it does lead to improved clinical outcomes when administered for 21 days after presentation with aSAH.

More recently, intrathecal administration of nimodipine has been explored as a treatment for vasospasm and DCI. This emerging treatment effectively prevents angiographic cerebral vasospasm, but the effect may be limited to vessels in close proximity to the drug administration or release site. Furthermore, this treatment has not yet been shown to improve long-term clinical outcomes.¹¹



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Other pharmacologic treatments have also failed to improve clinical outcomes significantly. For example, clazosentan is a selective endothelin-A antagonist that held promise as preventative treatment for DCI. The multicentric CONSCIOUS-1 randomized control trial showed that despite significant reductions in angiographic cerebral vasospasm, clazosentan did not decrease morbidity and mortality or improve functional outcome.¹² Recently, two double-blind, placebo-controlled phase 3 studies in Japan demonstrated that clazosentan significantly reduced the combined incidence of vasospasm-related morbidity and all-cause mortality post-aSAH, but has not yet been approved for treatment globally.¹³

The use of other pharmacologic treatments such as intravenous magnesium,¹⁴ statins,¹⁵ and intravenous milrinone¹⁶ also showed no long-term benefit in patients with aSAH. In aggregate, these studies strongly suggest the pathophysiological mechanism behind DCI is likely to extend beyond pure large vessel vasoconstriction.

Endovascular therapy (EVT) treatment of vasospasm and DCI consists of trans-arterial endovascular procedures that aim to improve cerebral artery vasospasm and cerebral perfusion. The two most performed EVT treatments are (1) trans-arterial vasodilator infusion and (2) cerebral artery angioplasty. Vasodilator infusion is commonly performed with calcium channel blocking medications (nicardipine and verapamil) or milrinone. These medications are infused through arterial catheters that are commonly positioned within the cervical internal carotid artery or vertebral artery, proximal to the regions of cerebral artery vasospasm. This treatment does result in an improvement in cerebral artery vasospasm, but these medications have a relatively short half-life and may result in significant hemodynamic instability during infusion.

More aggressive EVT treatments of vasospasm include angioplasty using a balloon microcatheter or stentriever device, which are often performed in conjunction with trans-arterial vasodilator infusion.¹⁷ These techniques require microcatheter and device placement within the cerebral arteries, which carries an increased risk of an ischemic stroke and vessel dissection or laceration. Angioplasty is effective in arterial dilatation, but it is limited to the treatment of proximal cerebral arteries, and it does not directly treat the more distal arterial bed, which may also be affected by vasospasm.

Overall, although the use of EVT treatment strategies is reasonable in patients with symptomatic cerebral vasospasm, as suggested by the most recent guidelines,¹⁰ future prospective and randomized studies are warranted to demonstrate the impact of these therapies on clinical outcomes. New treatment strategies that improve cerebral blood flow (CBF), cerebral perfusion, and long-term clinical outcomes are sorely needed.

Sympathetic innervation, CBF regulation, and a potential treatment for vasospasm and DCI

The cervical sympathetic trunk is located on both sides of the cervical spine and runs along the prevertebral fascia posteriorly and the longus colli muscle anteriorly. It is composed of the superior, the middle, the stellate, and inconstant vertebral ganglia¹⁸ (figure 1). The cervical and cerebral arteries are well innervated by sympathetic nerves. Sympathetic trunk stimulation results in constriction of these arteries, which, in turn, reduces CBF. By contrast, sympathetic trunk inhibition or ablation results in vasodilatation and improved CBF.¹⁹

Following aSAH, there is a massive activation of the sympathetic nervous system, which likely contributes to the development of vasospasm in these patients.²⁰ The cerebral arteries have

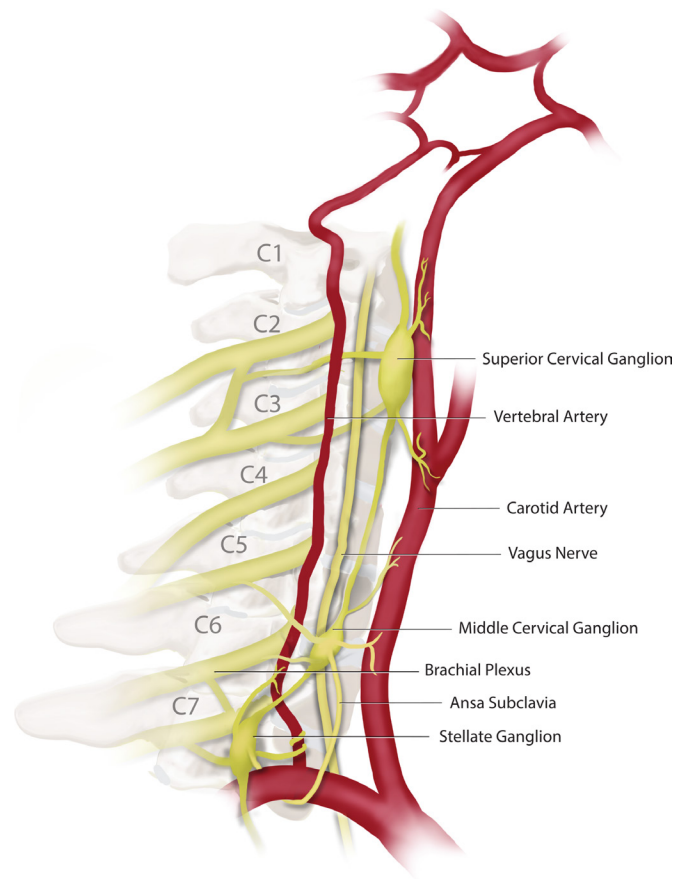


Figure 1 Anterior view of the neck where the cervical sympathetic trunk lies. Muscles and veins have been removed to show the ganglia of the cervical sympathetic trunk and their relationship to the cervical vertebrae and the vertebral and carotid arteries.

rich sympathetic innervation in the large cerebral arteries as well as within the smaller arteries and arterioles,¹⁹ which raises the possibility that sympathetic stimulation in aSAH patients may directly cause vasospasm that impacts the macro- and microcirculation of the brain.²¹ It also follows that sympathetic nerve blockade may release the vasoconstricting stimulus and improve CBF and cerebral perfusion (figure 2).

In 1936, Leriche²² described that a stellate ganglion block reversed cerebral vasoconstriction in a patient with cerebral vasospasm due to aSAH. More recently, Kim *et al*²³ demonstrated in an animal model that superior cervical ganglion stimulation resulted in 20–30% reduction in mean ipsilateral CBF and that prior injection of lidocaine to the cervical ganglion inhibited the effects of this stimulation and restored normal cerebral perfusion. However, sympathetic nerve block techniques are not widely performed for the treatment of vasospasm and DCI.

We conducted a review on cervical sympathectomy to treat vasospasm and DCI in humans after aSAH to define the state of the literature on this topic and to identify knowledge gaps to guide future studies. Table 1 summarizes the characteristics of the studies included in this review.

Evidence that CSB is effective in treating vasospasm

Experimental models of aSAH demonstrated that CSB results in vasodilatation due to a reduction in sympathetic tone in the cerebral arteries.^{24–26} Treggiari *et al*²⁷ performed a study in which patients with symptomatic vasospasm underwent a baseline digital subtraction angiography (DSA) followed by a CSB. After

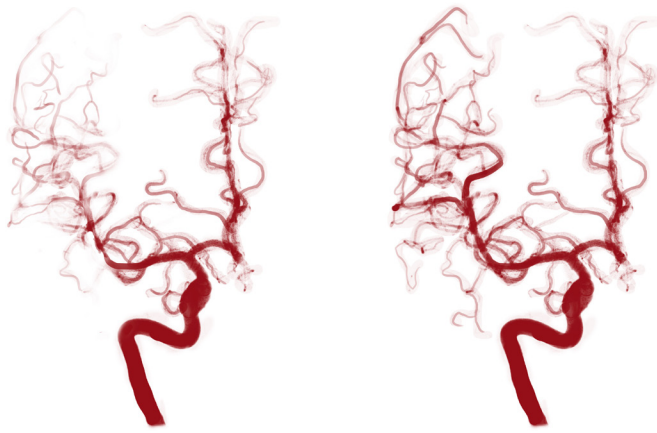


Figure 2 Digital image of the circle of Willis at digital subtraction angiography pre- (left side) and post- (right side) treatment showing the expected vasodilatation in the territory of the middle cerebral artery after a sympathetic block.

CSB, patients underwent a repeated DSA to assess for changes in cerebral artery caliber. Interestingly, DSA studies done after CSB did not demonstrate a significant difference in arterial diameter but detected a decreased filling time of the proximal intracranial carotid arteries on the blocked side and a reduced circulation time compared with baseline and compared with the opposite side. These results suggest that CSB may induce small artery vasodilation or other changes that improve CBF and cerebral perfusion. Pileggi *et al*²⁸ performed a similar study and detected distal circulation vasodilatation on CTA studies performed after CSB (figure 3). However, single-phase CTA is insensitive to cerebral perfusion given the technique's lack of temporal resolution, which is a limitation of these studies.

Samagh *et al*²⁹ insonated the middle cerebral artery (MCA) with transcranial Doppler (TCD) before and after CSB and observed a statistically significant reduction in velocities after CSB. Subjects in this study also underwent digital subtraction angiography, which demonstrated a significant increase in the mean vessel diameter measured at the mid-M1 segment of the MCA and at the mid-A1 segment of the anterior cerebral artery, and a decreasing trend in mean parenchymal filling time and mean venous sinus filling time after the sympathetic block, which also indicates vasodilatation of the microcirculation. Other studies have found reduced velocities in the MCA after a CSB, which is consistent with vasodilatation of this arterial bed after treatment.^{29–33} Collectively, these data suggest that CSB results in vasodilatation of the cerebral arteries. It remains uncertain whether the CSB vasodilatory predominantly affects proximal or distal arteries of the cerebral circulation.

An improvement in cerebral artery caliber is expected to increase CBF and cerebral perfusion. However, only one case report in humans has directly measured cerebral perfusion changes after CSB.³⁴ In this study, authors compared cerebral perfusion pre- and post-CSB on CT perfusion (CTP) studies. They found that CSB resulted in an improvement in cerebral perfusion, which is consistent with animal studies.²³ However, this study is confounded by the intra-arterial administration of a vasodilator before the CSB. In summary, the available evidence consistently points to cerebrovascular dilatation, preferentially in distal beds, with variable changes in large vessel diameter.

Evidence that a prophylactic CSB prevents DCI and improves clinical outcomes

The early evidence that CSB leads to cerebral artery dilatation and increased cerebral perfusion suggests that this technique may lead to a reduced risk of DCI and an increased likelihood of favorable clinical outcomes. Several single arm studies suggest that CSB leads to an immediate improvement in neurologic status and favorable rates of long-term clinical outcomes.

Treggiari *et al*²⁷ found an immediate improvement in neurologic status in DCI patients, which included complete reversal of neurological deficits in six out of nine patients. Jain *et al*³³ reported an improvement in Glasgow Coma Score 30 min after CSB and favorable long-term neurologic outcomes, as measured by the Glasgow Outcome Scale, in 73% of treated patients 6 months after aneurysm rupture. Samagh *et al*²⁹ found neurological improvement in 25% of patients receiving a CSB. Zhang *et al*³⁰ were the first to administer a CSB prophylactically, before the occurrence of DCI, in patients undergoing ruptured aneurysm treatment by neurosurgical clipping. The authors randomized patients to either standard medical therapy or ultrasound-guided CSB the day of surgery and on post-operative days (PODs) 2, 4, and 6. They measured velocities with TCD in the MCA in the basilar artery (BA), markers of inflammation and of brain injury the day before surgery and on PODs 1, 3, and 7. Velocities in the MCA and BA were the same at baseline in both groups and significantly increased from POD 1 to POD 7; nevertheless, these increases were significantly lower in the group of patients receiving a CSB ($P < 0.05$). The increase in velocities peaked at POD 7, with increases higher than 100% in the group not receiving a block, while in the CSB group the average increase was 50% compared with baseline. At the 6 months follow-up, 54% of patients in the CSB group had a favorable clinical course as measured by the Glasgow Outcome Scale compared with 32.6% in the control group ($P = 0.001$). However, the authors never diagnosed vasospasm and DCI. They detected increased TCD velocities compared with baseline values, which were higher in patients who did not receive a CSB, but they never distinctly diagnosed vasospasm by non-TCD imaging or DCI by clinical symptoms, which is a significant limitation of this study.

These studies are promising and suggest that CSB may lead to improved short- and long-term neurologic outcomes. However, most of these studies have a small sample size, and did not correlate imaging biomarkers of vasospasm and cerebral perfusion to clinical outcomes. Therefore, further research is needed to confirm if a CSB consistently improves neurological outcomes and by which mechanisms.

CSB technical considerations

The studies described above have varied slightly in the CSB technique, which introduces uncertainty as to the optimal method for performing the sympathetic block. Most authors report doing a stellate ganglion block,^{28–31 33} which is commonly performed at the level of the sixth or seventh cervical vertebrae, whereas others have described a superior cervical ganglion block.²⁷ These technical differences may seem relatively minor, but the anatomy and sympathetic innervation of the cerebral arteries is variable, which may impact the efficacy of the CSB. For example, there is evidence that the anterior cerebral circulation is innervated by sympathetic postganglionic fibers that originate from the superior cervical ganglion, whereas the posterior cerebral circulation derives its sympathetic innervation by postganglionic fibers originating from the stellate ganglion.¹⁹ Therefore, the anatomic targeting of the CSB may selectively impact the anterior versus posterior circulation (figure 1).

Table 1 Human studies characteristics, vessel diameter measurement and neurological findings

First author, year	Type of study	Number of patients, age	Block technique	Vessel diameter measurement	Time of vessel diameter measurement	Findings	Neurological changes
Treggiari <i>et al.</i> , ²⁷ 2003	Prospective, observational	9 41±17	Fluoroscopy	DSA	To diagnose CAV and repeated after the block	Arterial delay, from 0.9±0.6 to 0.2±0.3 s (P<0.05), and parenchymal defect from 2.5±1.5 to 1.1±1.5 s (P<0.05) after the block. Unchanged vessel diameter	Clinical improvement with complete symptom resolution in 6 patients
Jain <i>et al.</i> , ³³ 2011	Prospective, no control	15 45.5±13.6	Surface landmarks using anterior paratracheal approach	TCD	Before the block, 10 and 30 min, 2-, 6, 12 and 24 hours after the block	Ipsilateral to CSB: mean MCA velocity, from 134 (8, SE) to 110 (6) at 6 hours and 113 (6) cm/s (P<0.001) at 24 hours after the block; mean ACA velocity, from 106 (6) to 94 (5) at 6 hours and 96 (5) cm/s (P<0.001) at 24 hours after the block. Contralateral to CSB: mean MCA velocity, from 96 (4) to 85 (4) cm/s (P<0.001) at 6 hours; mean ACA velocity from 74 (5) to 69 (5) cm/s (P<0.001) at 6 hours, in both vessels persisting for 12 hours after the block	Improvement in GCS after 30 min (p=0.002); 73% of patients had favorable outcome as measured by GOS at 6 months after SAH
Wendel <i>et al.</i> , ³¹ 2020	Retrospective	37 49.9±11.1	Surface landmarks using anterior paratracheal approach	TCD	CBFV before the block, and at 2 and 24 hours afterwards	Ipsilateral MCA velocity: from 160±28 to 127±34 at 2 hours to 137±38 cm/s at 24 hours after the block corresponding to a 20% and 15% reduction	24 of the 37 patients significantly disabled (GOS ≤3) at ICU discharge, and moderately disabled (GOS 4) at 6 months follow-up
Pileggi <i>et al.</i> , ²⁸ 2021	Retrospective	10 Mean age 50.2 years, range 37–66	Fluoroscopy	DSA	Before the block in all patients, and in selected patients after the block	Angiographic vasodilation on the distal circulation	Average clinical outcome measured by modified Rankin Scale at discharge was 3 indicating moderate disability
Zhang <i>et al.</i> , ³⁰ 2021	Randomized controlled trial	SGB (n=50) 51.43±2.22. Non-SGB (n=52) 53.76±1.74	Ultrasound	TCD in the MCA and basilar arteries	The day before surgery (POD 0) and on POD 1-3-7	MCA and basilar arteries' velocities were higher on POD 1 and POD 3 compared with POD 0 in both groups, but this increase was lower in the SGB group (P<0.05)	Better neurologic prognosis score and neurological function 6 months after surgery in patients who received an SGB
Samagh <i>et al.</i> , ²⁹ 2022	Prospective, observational	20	Ultrasound	TCD and DSA	Before and after the block	TCD: reduction in ipsilateral systolic MCA velocity (from 150±22 to 140±24 cm/s, P=0.005), mean MCA velocity (from 120±23 to 108±25 cm/s, P=0.025), and Lindegaard ratio (from 2.57±0.46 to 2.34±0.50, P=0.022) after a CSB. DSA: increase in the mean vessel diameter measured at the mid-M1 segment of ACA (from 0.109±0.049 cm to 0.124±0.0517 cm, P=0.002), mid-A1 segment of MCA (from 0.174±0.046 cm to 0.189±0.0415 cm, P=0.003); decreased mean parenchymal filling time (from 3.18±0.37 s to 3.13±0.36 s, P=0.163) and venous sinus filling	Neurological improvement in 5 (25%) patients

ACA, anterior cerebral artery; aSAH, aneurysmal subarachnoid hemorrhage; CAV, cerebral blood flow velocity; CSB, cervical sympathetic block; DSA, digital subtraction angiography; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Score; ICU, intensive care unit; MCA, middle cerebral artery; POD, post-operative day; SAH, subarachnoid hemorrhage; SGB, stellate ganglion block; TCD, transcranial Doppler.

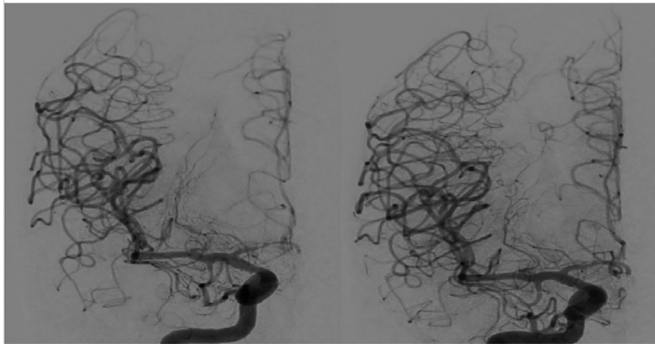


Figure 3 Cerebral angiography in arterial phase before (left image) and 20 min after (right image) a left stellate ganglion block. The results of the post-block angiography are confounded by the intra-arterial injection of nimodipine after the block. The left internal carotid artery arteriography shows improvement of A1 segment caliber and better opacification of anterior cerebral artery territory.

Cadaveric and imaging studies have shown a considerable anatomic variation in the localization of the cervical sympathetic ganglia compared with the transverse processes of the cervical vertebrae with respect to the most common ones reported.³⁵ In practice, it is challenging to selectively perform a CSB at a specific ganglion, which is partially influenced by variable anatomy. In theory, if a CSB is accurately performed and the local anesthetic is delivered within the plane deep to the prevertebral fascia, between the longus capitis and longus colli muscle, the local anesthetic will diffuse to the nearby sympathetic trunk which is contained within this space.

An injection midway at the sympathetic trunk, at C6 at the level of the middle cervical ganglion, offers multiple advantages. The middle cervical ganglion lies in proximity to the anterior tubercle of C6, which is the more prominent cervical tubercle and therefore easier to visualize on ultrasound (figure 4). Anesthetic injection at the C6 level should block all the preganglionic fibers ascending from the spine such that sympathetic synapses located more cranially at the level of the superior cervical ganglion will be blocked. Thus, a CSB performed at the C6 level should effectively block sympathetic innervation of the anterior circulation. In addition, there is a high likelihood that local anesthesia administered at the C6 level will diffuse inferiorly to the C7 level, where the stellate ganglion is located. Therefore, a C6 CSB will also likely inhibit the stellate ganglion, such that the postganglionic fibers that enervate the posterior circulation will be blocked along with the anterior circulation.

By contrast, a selective superior cervical ganglion block may spare the fibers that enervate the posterior circulation. Recently, Kim *et al*²³ showed that stimulation of the superior cervical ganglion results in a global reduction of ipsilateral perfusion, as measured by CTR, that is isolated to the anterior circulation territory. The posterior circulation was therefore not affected by this CSB of the superior cervical ganglion. There is a need for additional studies to determine how CSB anatomic location influences cerebral perfusion in the anterior versus posterior circulation of the brain.

Modality of performing the technique

CSB may be performed using a variety of anatomic and image-guided techniques. Anatomic landmark,^{31 33} ultrasound guidance,^{29 30} fluoroscopy,^{27 28} or open surgical resection³⁶ may be used for CSB localization, and the way the CSB is performed may influence the efficacy of the technique. Ultrasound imaging

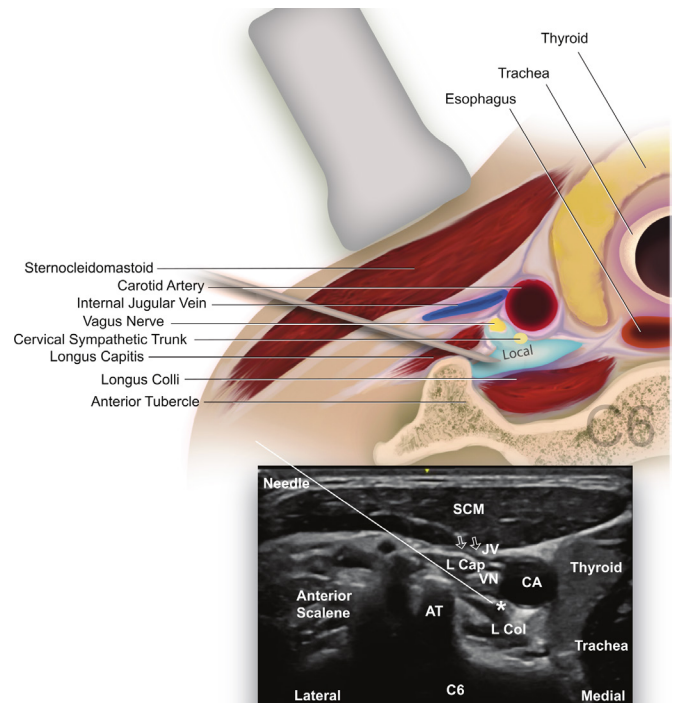


Figure 4 Cross-sectional view of the anatomical and ultrasound image structures at the sixth cervical vertebrae level where the block is commonly performed. The short axis ultrasonogram at C6 shows: SCM, sternocleidomastoid muscle; V, vagus nerve; CA, carotid artery; JV, compressed internal jugular vein (hollow arrows); * indicates the anatomical location where the cervical sympathetic trunk lies, not visualized with ultrasound imaging. The needle advances at the level of the anterior tubercle (AT) to locate the cervical sympathetic trunk at the middle cervical ganglion located between the longus capitis muscle (L Cap) and the longus colli muscle (L Col).

has revolutionized the field of regional anesthesia and led to improved efficacy and safety of CSB due to improved real-time visualization of the anatomy being targeted by the procedure.³⁷ In addition, ultrasound allows for the CSB procedure to be safely performed at the bedside in the intensive care unit, with rapidity and minimal equipment, supplies, costs, and risks. Although there are no data that have compared the efficacy of the different execution modalities of a CSB, anesthesiologists today prefer to use ultrasound guidance to perform nerve blocks as there is evidence that nerve blocks performed by ultrasound guidance are superior in terms of efficacy and fewer minor complications reported.³⁸

Drug type, drug volume and drug delivery modality

It is likely that the dose and delivery modality of the CSB anesthetic influences the efficacy and durability of the block. However, how these variables influence the impact of CSB on vasospasm and DCI has not been well described. Previous studies of CSB in aSAH patients are heterogeneous in terms of drug type, dose and volume. Studies used either 5–10 mL of 0.5%^{27 28 33} or 8–10 mL of 0.2% bupivacaine,³¹ or 0.375% and 0.5% ropivacaine.³⁰ Some authors added clonidine as an adjuvant to the local anesthetic to prolong the effect of a single shot injection,^{27 31} and one group of authors used an indwelling catheter infusing 0.2% ropivacaine at 5 mL/hour²⁸ to prolong the effect of the block.

In addition, how the manner of drug delivery by a single injection versus a continuous infusion via an indwelling catheter influences vasospasm and DCI is poorly described. Two prior

studies describe placement of an indwelling periganglionic catheter for continuous CSB,^{28–39} which may reduce the need for sequential CSB procedures given the relatively short half-life of the local anesthetic medications used in these procedures.

Whether infusion catheter placement is advantageous in vasospasm and DCI reduction or increases the risk of the CSB technique in aSAH patients requires further study.

Unilateral versus bilateral CSB

Vasospasm and DCI affect the entirety of the cerebral circulation, although vasospasm is often more severe in the region immediately adjacent to the ruptured aneurysm. The diffuse nature of vasospasm and DCI suggests that performing a bilateral CSB may be a superior technique, although unilateral versus bilateral CSB has not been directly compared in this patient population. However, bilateral stellate ganglion blocks may increase the risk of a profound bradycardia due to blockade of the cardioaccelerator fibers that originate from the stellate ganglia.⁴⁰ A block attempting to be selective for the middle/superior cervical block will not have this side effect. Additional safety and feasibility studies performing bilateral CSB in patients with ruptured cerebral aneurysms are warranted.

CSB complications

In general, CSB complications are minor and self-limited. A study on 2000 stellate ganglion blocks performed using anatomic landmarks found no serious complications.⁴¹ Nevertheless, technical complications such as injury to the nearby nerves, such as the vagus nerve or the brachial plexus roots, and nearby viscera, such as the trachea and esophagus, during insertion of the needle have been reported. The use of ultrasound minimizes these risks due to real-time visualization of the needle. Non-specific complications of nerve blocks include infections, puncture of the dura, and intravascular injections of local anesthetic leading to toxicity, the latter of which is easily avoidable with ultrasound guidance.

Roadmap for future studies

The available evidence for CSB as an effective preventative and therapeutic treatment for vasospasm and DCI is promising. However, this understudied field remains in its infancy and requires more rigorous scientific exploration. Future studies should focus on (1) CSB technique standardization, (2) improving our understanding of how CSB improves cerebral perfusion in humans, and (3) providing stronger evidence that the technique improves immediate and long-term neurologic outcomes.

Additional knowledge is also required to understand how CSB might be integrated with conventional EVT treatment of vasospasm and DCI. Does CSB compliment or replace intra-arterial vasodilator infusion and angioplasty? Can CSB be used to reduce significantly the likelihood of developing vasospasm and DCI when performed shortly after presentation with aSAH? Well-conceived prospective studies are needed to address these pressing questions.

CONCLUSIONS

CSB is a minimally invasive, safe technique that may provide a new treatment for vasospasm and DCI in patients who have suffered cerebral aneurysm rupture. The initial studies described in this review suggest great promise for CSB, but there is significant work to do before the technique can be more widely performed in aSAH patients.

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ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Gregory Albers

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

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ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Anna Maria BOMBardieri

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

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ICMJE DISCLOSURE FORM

Date: 11/16/2022

Your Name: Jeremy Heit, MD, PhD

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

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2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None <table border="1" style="width: 100%; margin-top: 5px;"> <tr> <td style="width: 60%;">R01 NS075209</td> <td style="width: 40%;">Institution</td> </tr> <tr> <td>R01 NS121720-01</td> <td>Institution</td> </tr> <tr> <td>R01 NS11351704</td> <td>Institution</td> </tr> <tr> <td>R01 EB032417-01A1</td> <td>Institution</td> </tr> </table>	R01 NS075209	Institution	R01 NS121720-01	Institution	R01 NS11351704	Institution	R01 EB032417-01A1	Institution
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ICMJE DISCLOSURE FORM

Date: 11/18/2022

Your Name: Marco Pileggi

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): jnis-2022-019838

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Date: 11/19/2022

Your Name: Samuel Rodriguez

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

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ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Gary Steinberg

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

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1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; height: 40px; margin-top: 5px;"> <tr><td style="width: 60%;"></td><td style="width: 40%;"></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table> <small style="margin-top: 5px;">Click the tab key to add additional rows.</small>						
Time frame: past 36 months								
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; height: 40px; margin-top: 5px;"> <tr><td style="width: 60%;"></td><td style="width: 40%;"></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>						
3	Royalties or licenses	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; height: 40px; margin-top: 5px;"> <tr><td style="width: 60%;"></td><td style="width: 40%;"></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>						

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	<input type="checkbox"/> None	
		Sanbio – consultant	Personal
		Zeiss – consultant	
		Surgical Theatre – consultant	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input type="checkbox"/> None	
		Peter Lazic, US – patents	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or	<input checked="" type="checkbox"/> None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
	advocacy group, paid or unpaid		
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	
<p>Please place an "X" next to the following statement to indicate your agreement:</p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Gregory Albers

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. “Related” means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author’s relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

	Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)						
Time frame: Since the initial planning of the work								
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	<div style="border: 1px solid black; padding: 5px;"> <input checked="" type="checkbox"/> None </div> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr><td style="height: 20px;"> </td><td style="width: 30%;"></td></tr> <tr><td style="height: 20px;"> </td><td></td></tr> <tr><td style="height: 20px;"> </td><td style="text-align: right; font-size: small;">Click the tab key to add additional rows.</td></tr> </table>						Click the tab key to add additional rows.
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Time frame: past 36 months								

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None 	
3	Royalties or licenses	<input checked="" type="checkbox"/> None 	
4	Consulting fees	<input type="checkbox"/> None 	
		SchemaView	equity
		Genetech	consulting fees
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None 	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None 	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None 	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	

Please place an “X” next to the following statement to indicate your agreement:

	Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
<input checked="" type="checkbox"/>	I certify that I have answered every question and have not altered the wording of any of the questions on this form.	

ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Anna Maria BOMBardieri

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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Time frame: past 36 months								
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; height: 40px; margin-top: 5px;"> <tr><td style="width: 60%;"></td><td style="width: 40%;"></td></tr> <tr><td></td><td></td></tr> <tr><td></td><td></td></tr> </table>						
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4	Consulting fees	<input checked="" type="checkbox"/> None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	
<p>Please place an "X" next to the following statement to indicate your agreement:</p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

ICMJE DISCLOSURE FORM

Date: 11/16/2022

Your Name: Jeremy Heit, MD, PhD

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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Time frame: Since the initial planning of the work														
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; height: 40px; margin-top: 5px;"> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> </table>												
Time frame: past 36 months														
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input type="checkbox"/> None <table border="1" style="width: 100%; margin-top: 5px;"> <tr> <td style="width: 60%;">R01 NS075209</td> <td style="width: 35%;">Institution</td> <td style="width: 5%;"></td> </tr> <tr> <td>R01 NS121720-01</td> <td>Institution</td> <td></td> </tr> <tr> <td>R01 NS11351704</td> <td>Institution</td> <td></td> </tr> <tr> <td>R01 EB032417-01A1</td> <td>Institution</td> <td></td> </tr> </table>	R01 NS075209	Institution		R01 NS121720-01	Institution		R01 NS11351704	Institution		R01 EB032417-01A1	Institution	
R01 NS075209	Institution													
R01 NS121720-01	Institution													
R01 NS11351704	Institution													
R01 EB032417-01A1	Institution													
3	Royalties or licenses	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; height: 40px; margin-top: 5px;"> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> </table>												

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	<input type="checkbox"/> None	
		Medtronic	Personal
		MicroVention	Personal
		iSchemaView	Personal
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input type="checkbox"/> None	
		iSchemaView	Personal
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input type="checkbox"/> None	
		Board of Directors, Society of Neurointerventional Surgery	Personal
		Board of Directors, Society of Neurointerventional Surgery Foundation	Personal

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	<input checked="" type="checkbox"/> None	
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
<p>Please place an "X" next to the following statement to indicate your agreement:</p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

ICMJE DISCLOSURE FORM

Date: 11/18/2022

Your Name: Marco Pileggi

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): jnis-2022-019838

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)						
Time frame: Since the initial planning of the work									
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr><td style="width: 50%; height: 20px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> <tr><td style="height: 20px;"></td><td style="text-align: right; font-size: small;">Click the tab key to add additional rows.</td></tr> </table>						Click the tab key to add additional rows.	
	Click the tab key to add additional rows.								
Time frame: past 36 months									
2	Grants or contracts from any entity (if not indicated in item #1 above).	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr><td style="width: 50%; height: 20px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> </table>							
3	Royalties or licenses	<input checked="" type="checkbox"/> None <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr><td style="width: 50%; height: 20px;"></td><td style="width: 50%;"></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> <tr><td style="height: 20px;"></td><td></td></tr> </table>							

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4	Consulting fees	<input checked="" type="checkbox"/> None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	<input checked="" type="checkbox"/> None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	<input checked="" type="checkbox"/> None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	<input checked="" type="checkbox"/> None	
13	Other financial or non-financial interests	<input checked="" type="checkbox"/> None	
<p>Please place an "X" next to the following statement to indicate your agreement:</p> <p><input checked="" type="checkbox"/> I certify that I have answered every question and have not altered the wording of any of the questions on this form.</p>			

ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Samuel Rodriguez

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	<input type="checkbox"/> None	
		Apple Inc	personal
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input checked="" type="checkbox"/> None	
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ICMJE DISCLOSURE FORM

Date: 11/19/2022

Your Name: Gary Steinberg

Manuscript Title: Percutaneous Cervical Sympathetic Block to treat Cerebral Vasospasm and Delayed Cerebral Ischemia: A Review of the Evidence

Manuscript Number (if known): 2022-019838.R1

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Time frame: past 36 months								
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		Sanbio – consultant	Personal
		Zeiss – consultant	
		Surgical Theatre – consultant	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
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7	Support for attending meetings and/or travel	<input checked="" type="checkbox"/> None	
8	Patents planned, issued or pending	<input type="checkbox"/> None	
		Peter Lazic, US – patents	
9	Participation on a Data Safety Monitoring Board or Advisory Board	<input checked="" type="checkbox"/> None	
10	Leadership or fiduciary role in other board, society, committee or	<input checked="" type="checkbox"/> None	

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