REVIEW ARTICLE

Current Status and Recommendations in Multimodal Neuromonitoring

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Abstract

Every patient in neurocritical care evolves through two phases. Acute pathologies are addressed first. These include trauma, hemorrhagic or ischemic stroke, or neuroinfection. Soon after, the concentration shifts to identifying secondary pathologies like fever, seizures, and ischemia, which may exacerbate the brain injury. Frequent bedside examinations are not sufficient for timely detection and prevention of secondary brain injury (SBI) as per the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care. Multimodality monitoring (MMM) can help in tailoring treatment decisions to prevent such a brain injury. Multimodal neuromonitoring involves data-guided therapeutic interventions by employing various tools and data integration to understand brain physiology. Monitors provide real-time information on cerebral hemodynamics, oxygenation, metabolism, and electrophysiology. The monitors may be invasive/noninvasive and global/regional. We have reviewed such technologies in this write-up. Novel themes like bioinformatics, clinical research, and device development will also be discussed.

Keywords: Brain tissue oxygen, Cerebral metabolism, Data integration, Quantitative EEG.

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Introduction

Acute brain injury (ABI) frequently involves alteration of the mental status. This limits the yield of the clinical neurological examination. Clinical findings may trail the shifts in cerebral physiology. This leads to a delay in detection only after catastrophic damage has set in. These may be cognitive impairment, delayed cerebral ischemia (DCI), and motor disability.[1] Accordingly, frequent bedside examinations are deemed insufficient for timely detection and prevention of secondary brain injury (SBI) as per the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care. Examination must be coupled with multimodality monitoring (MMM) along with advanced bioinformatics tools for better outcomes.[2,3]

Neurophysiology goes through dynamic changes after a primary neurologic injury. Multimodality monitoring assimilates data from multiple devices in real time. The goal is to identify such fluctuations and indicate the need for intervention to prevent SBI like cerebral hypoperfusion or ischemia due to intracranial pressure (ICP) surges, cerebral hypoxia, cerebral hypoglycemia, or excitotoxic damage due to recurrent or prolonged seizures.[4,5]

The proposed roles for MMM are the following:

- Tracking, prevention, and treatment of the cascade of SBI
- Monitoring of patients with the impaired Glasgow coma scale (GCS) of less than 9 or those with intraparenchymal contusions/subarachnoid hemorrhage (SAH)/intracerebral hemorrhage (ICH) brain computerized tomography (CT). These patients may have an unreliable clinical examination
- Providing an understanding of the SBI-related pathophysiologic mechanisms to develop preventive and abortive therapies
- Integration of data from clinical examination, neuroimaging, and MMM, which would yield a patient-specific real-time picture for targeted management
- Prognostication[6,7]

Various MMM based on function are listed in Table 1.[7]

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Multimodal Monitoring

Table 2 shows various neuromonitoring modalities, normal values, and their clinical significance.[3]

Intracranial Pressure

The commonest monitored parameters in ABI are ICP and cerebral perfusion pressure (CPP). Acute brain injury causes a large increase in intracranial volumes due to cerebral edema or expanding hematoma. This causes reduced cerebral blood flow (CBF), ischemia, followed by cerebral herniation.[8] Overall prognosis is worse.[9] Protocol recommends ICP monitoring in ABI where clinical or imaging features suggest a risk of elevated ICP.[10] Additionally, CPP and assessment of intracranial compliance, cerebrovascular reactivity, and autoregulatory status can be monitored.[11,12]

Ventriculostomy using extraventricular drain (EVD) remains the gold standard ICP monitor for global ICP.[10,13] Extraventricular drain is rezeroed after placement to minimize drift.[13] It also allows

cerebrospinal fluid drainage in patients who have hydrocephalus. However, insertion in compressed or displaced ventricles can be difficult. The fluid column can get obstructed by a blood clot, leading to inaccurate measurements. Further, the transducer should be maintained at a fixed reference point relative to the patient's head. Extraventricular drain placement may cause significant clinical bleeding in <1% cases and EVD-related infections in 5–15%.[14]

For traumatic brain injury (TBI) who need only ICP and CPP monitoring, and are not at risk of hydrocephalus, the intraparenchymal monitors are the recommended alternative.[10] Their placement is easier and they can provide continuous monitoring compared to EVD. Piezoelectric strain gauge and fiberoptic sensors constitute the current technology.[3] In focal lesions with mass effect, an interhemispheric variation of >10 mm Hg is known. Therefore, it is vital to position the sensors close to the area at risk and so is confirmation by CT imaging.[15] Limitations of intraparenchymal monitors are the cost and no prospect of recalibrating the measurements, which drift with time. With respect to other invasive types of ICP monitors such as subdural, subarachnoid, and epidural bolts, limited accuracy and daily drifts preclude their use in clinical practice.[1,3]

Tympanic membrane displacement to measure ICP is investigational. It evaluates how the perilymph and cerebrospinal fluid communicate via the perilymphatic duct.[16] Transcranial Doppler with pulsatility index, pupillometry, and ultrasound measurement of optic nerve sheath diameter are other noninvasive tools. However, they are less accurate compared to invasive monitoring.[17]

Table 1: Various multimodality neuromonitorings based on function

	Parameter	*Global physiology*	*Local physiology*
1	Cerebral flow-directed techniques	ICP, CPP	TCD, TDF
2	Cerebral autoregulation	PRx, Mx, ORx	–
3	Cerebral oxygenation-directed techniques	$SjvO_2$	$PbtO_2$, NIRS
4	Reflecting cerebral metabolism	S100B, NSE	Microdialysis, imaging
5	Reflecting cerebral global function	EEG, qEEG	–

cEEG, continuous EEG; CPP, cerebral perfusion pressure; EEG, electroencephalography; GCS, Glasgow coma scale; ICP, intracranial pressure, NIRS, near-infrared spectroscopy; NSE, neuron-specific enolase; ORx, oxygen reactivity index; $PbtO_2$, brain tissue oxygen partial pressure; PRx, pressure reactivity index; Mx, mean velocity index; qEEG, quantitative EEG; $SjvO_2$, jugular venous oxygen saturation; TCD, transcranial Doppler; TDF, thermal diffusion flowmetry

Table 2: Multimodality parameters: commonly used measurement devices, physiologic ranges, threshold at which early goal therapy should be considered, and clinical significance[3]

Modality	*Means of monitoring*	*Physiologic range*	*Threshold*	*Clinical significance*
ICP	Intraparenchymal monitor, intraventricular monitor (EVD)	<20 mm Hg	>20–25 mm Hg	Marker of cerebral edema and impending herniation
CPP		60–70 mm Hg	<60 mm Hg	Indirect surrogate of CBF, guides treatment of intracranial hypertension to optimize perfusion
CBF	(1) TCD	Mean flow velocities: MCA 30–75 cm/second, ACA 20–75 cm/second, PCA 15–55 cm/second, LR < 3	MCA mean flow velocity >200 cm/second, LR > 6	Detection of vasospasm and DCI in SAH, differentiates hyperemia from vasospasm, indicative of regional cerebral ischemia
	(2) TDP	50 mL/100 g/minute	<20 mL/100 g/minute	
Cerebral oxygenation	Jugular venous, oximetry	50–80%	<50% or >80%	Indicative of global ischemia or hyperemia and tissue extraction of oxygen, indicative of regional hypoxia/hypoperfusion
Cerebral metabolism	Microdialysis	Glucose 0.4–4.0 µmol/L	<0.4	Indicative of brain energy supply and demand
	Lactate 0.7–3.0 µmol/L	>3.0		
	Lactate to pyruvate ratio <20	>40	Elevated LPR indicative of ischemia, anaerobic metabolism	
	Glutamate 2–10 µmol/L	>10	Increased glutamate and lactate are earliest markers of ischemia followed by increased glycerol	
	Glycerol 10–90 µmol/L	>90		

TCD, transcranial cranial doppler; TDP, thermal diffusion probe; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; SAH, subarachnoid hemorrhage; LR, Lindegaard ratio; LPR, lactate to pyruvate ratio

Cerebral Autoregulation Monitoring

Dynamic cerebral autoregulation monitoring allows bedside calculation of optimal mean arterial pressure (MAP) and optimal CPP by noninvasive and invasive methods, respectively.[1] Surrogates of CBF can be obtained using noninvasive tools such as continuous transcranial cranial doppler (TCD), near-infrared spectroscopy (NIRS), and ultrasound-tagged near-infrared spectroscopy (UT-NIRS) or invasive tools (brain tissue oxygen monitors and ICP monitors).[1,18]

Cerebral Perfusion Pressure

The difference between MAP and ICP is CPP. It corresponds to the pressure gradient that drives CBF, and hence oxygen and metabolite delivery.[19] In a study involving acute TBI, fatal outcomes increased when CPP was below the optimal level, whereas CPP value greatly exceeding resulted in severe disability.[20] Thus, for favorable outcomes, one not only has to prevent hypoperfusion but also hyperperfusion by targeting optimal CPP.[1] However, in another study, only two-third patients demonstrated an optimal CPP.[21] In other studies where management was guided by target CPP rather than ICP, the outcome has not improved.[22,23]

Index of Pressure Reactivity

An uninjured brain can maintain a fairly constant CBF despite fluctuations in CPP. This is facilitated by varying intracerebral vessel caliber. This adaptive characteristic of static autoregulation is reflected by pressure reactivity (PRx).[1,3] Pressure reactivity measures the correlation between arterial blood pressure and ICP waves. Pressure reactivityis represented on a scale as a correlation coefficient (from +1.0 to −1.0). A negative value suggests intact autoregulation whereas a positive PRx value suggests impaired autoregulation. Studies show that the mortality rate in severe TBI is proportionate to a PRx positive value.[24] Mortality has shown to be lower when the PRx value is <0.25 (20% vs 69%).[24,25]

Other Indices of Cerebral Autoregulation

Indices such as the mean velocity index, which is based on CPP, and the autoregulatory reactivity index have not been validated as yet.[1,26]

Electroencephalography

Epileptogenic derangements in ABI like elevated excitatory amino acids and neurotransmitters[27] and hyperglycolysis may trigger seizures.[28] Around 5–15% of patients can have nonconvulsive status epilepticus (NCSE) in 5–20%.[29] Patients with ICH have seizures more often that in AIS[30] probably because extravasated iron is potentially proconvulsive.

Like convulsive seizures, non-convulsive seizures (NCSz) also lead to a state of cerebral hypoxia with an elevation of intracellular calcium, oxygen free radicals, and intracellular osmolality. This leads to neuronal swelling. There is a failure of ATP production and cell death. Cerebral edema and midline shift increases and eventually leads to a worse outcome. Numerous toxic metabolites like glutamate, neuron-specific enolase, and lactate to pyruvate ratio (LPR) are increased in NCSz. Follow-up magnetic resonance imaging (MRI) shows that hippocampal atrophy[31–33] is seen in NCSz. However, ironically, no adequately powered trials have demonstrated the positive impact of treating NCSz or NCSE.[1,29]

In ABI, clinical seizures may be in 25%, while nearly 50% of patients show subtle clinical findings, such as oral or ocular movements and/or gaze deviation.[34] Thus, in a comatose patient, NCSz would go unrecognized if not for EEG monitoring.[35] The sensitivity of an intermittent EEG to diagnose NCSz in comatose patients is 50%[36] when compared to a sensitivity of >90% on a 48-hour continuous EEG (cEEG).[37] Besides seizures, certain EEG patterns like broad repetitive slow waves correlate with the occurrence of vasospasm in SAH. This is where quantitative EEG (qEEG) is beneficial as it can analyze raw EEG data of several hours. It does this by deploying compressed spectral array and presents the data in a graphical form.[1,18]

The role of EEG in early detection of DCI in SAH is well established. As the CBF drops, faster frequencies decrease followed by a gradual increase in slower frequencies. For detection of DCI in SAH, alpha/delta ratio, power, and percent alpha variability can be utilized.[17,38,39] Burst suppression pattern is another poor prognostic factor. Thalamic injury in TBI patients is associated with an impaired percent alpha variability on qEEG. It heralds poor long-term outcomes.[40] Recovery of consciousness in TBI, cerebrovascular disease, or anoxia can be expected when EEG reactivity is present.[41]

Invasive cEEG monitoring can identify seizures that are not detectable by scalp electrodes. Although invasive electrodes like the subdural strip electrodes or intracortical depth electrodes can be placed at the bedside,[29] their use remains to be validated.[3]

Use of cEEG monitoring in ICU is limited due to high cost, nonavailability of technicians to apply and maintain electrodes, considerable ICU-related EEG artifacts, and availability of physicians for a timely interpretation of the EEG.[42] Devices for automated seizure detection and remote access for EEG viewing are being developed to overcome these limitations.[43]

Somatosensory Evoked Potential

Continuous somatosensory evoked potential (SSEP) monitoring is useful for prognostication. In postanoxic coma, absence of a cortical SSEP response bilaterally portends poor outcome, as does a prolonged central conduction time (CCT). In SAH, CCT prolongation correlates to transient neurological deficit. An added advantage is that prolongation precedes the development of such deficits.[44]

Other Evoked Potentials

Brainstem auditory-evoked response is a measure of pontomesencephalic integrity. Early changes in V waves and V latency occur in transtentorial herniation or increased ICP.[45] Thus, brainstem compression in comatose patients in ABI can be potentially monitored. Middle latency auditory-evoked potentials have proven to better predict favorable outcome ABI or SBI than cortical potentials of SSEP.[46]

Jugular Venous Oxygen Saturation

Assuming that arterial hemoglobin saturation and concentration remain stable, jugular venous oxygen saturation ($SjvO_2$) reflects the difference between cerebral oxygen supply and demand. For $SjvO_2$ monitoring, a fiber optic catheter is inserted in the retrograde direction at the origin of the internal jugular vein preferably in the dominant vein. Jugular venous oxygen saturation measurement allows the assessment of global oxygenation. Catheter tip at the level of the bodies of C1/C2 on lateral neck radiograph suggests correct placement.[47,48] Complications include infection, catheter misplacement, elevated ICP, thrombosis of the jugular vein, pneumothorax, and the need for frequent recalibrations.[1,47] Another limitation is that $SjvO_2$ may miss critical regional ischemia as it is a global, flow-weighted measure.[1,7]

Desaturation to <50% suggests ischemia. Desaturation that is sustained (>10 minutes) portends poor outcome in TBI.[49] Conversely, $SjvO_2$ above 75% represents hyperemia or infarcted tissue. Jugular venous bulb oximetry also facilitates sampling for the measurement of arterial-jugular venous oxygen content difference ($AVDO_2$). It can be used to monitor perfusion status. Global cerebral ischemia is suspected with $AVDO_2$ above 9 mL/dL and hyperemia if >4 mL/dL.[3] However, its accuracy has been challenged and so it may serve as a supplement to ICP monitoring.[18]

Cerebral Microdialysis

Cerebral microdialysis (CMD) allows for the quantification of metabolic intermediaries, substrates, and neurotransmitters like glucose, glutamate, lactate, and pyruvate. The CMD catheter is comprised of an inlet and outlet that join at a semipermeable membrane tip. A perfusate solution, which approximates the cerebrospinal fluid in composition, is infused in it. This allows for frequent sampling of dialysate.[1] Catheter placement for focal brain injuries is done perilesionally, for diffuse TBI in the right frontal region, and in the anterior cerebral artery and middle cerebral artery watershed region or region of vasospasm ipsilateral to the aneurysm rupture for SAH. Glucose <0.8 mM and LPR >40 warrant intervention.[50] A low interstitial glucose level indicates a deficient glucose delivery.[51] Compared to lactate alone, LPR is a more specific measure of cerebral ischemia.[52] Glutamate level elevation is seen in TBI[53,54] and SAH.[55] They represent cerebral ischemia and may herald a poor outcome.[56] Elevated glutamate levels can also cause seizures.[57] Glycerol elevation results from excess degradation of cell membrane phospholipid breakdown.[51] Like glutamate, glycerol elevation also correlates with ischemia and poor outcomes in TBI[58,59] and SAH.[55,60]

Cerebral microdialysis can also predict SBI. A study of patients of aneurysmal SAH found that an increase in the lactate/glucose ratio and LPR occurred 11 to 13 hours before the symptoms of delayed ischemic neurologic deficits developed.[61] A study for confirming vasospasm in asymptomatic SAH patients has favored CMD when compared to TCD or angiography.[62] In severe TBI patients, changes in CMD occur ahead of ICP elevation.[63]

Cerebral microdialysis can also guide insulin therapy and avoid hypoglycemia by monitoring cerebral metabolism.[64] While initiating enteral feeds, CMD can also monitor cerebral glucose.[65] Evidence suggests that neuroglycopenia in TBI patients portends poor outcomes.[66] A tightly controlled blood glucose control between 80 mg/dL and 120 mg/dL resulted in a reduction of cerebral glucose, and increased mortality in severe brain injury.[67] Cerebral microdialysis can potentially help in identifying the progression of ischemic stroke,[68] measurement of drug level like antibiotics or anticonvulsants, and may also lead to the discovery of new biomarkers.[69,70]

Limitations of CMD include the time-consuming procedure of drawing the sample, only a few cubic millimeters sample can be collected, and catheter placement influences the result. But most importantly, normal values and cut-offs for various substrates are not defined to guide ongoing therapy. At best, CMD can be combined with other MMM.[1]

Brain Oxygenation

Brain oxygenation is a surrogate of CBF. It can delineate tissue that is at risk for ischemia when it is used in conjunction with metabolic parameters.[3] Modalities like positron-emission tomography, MRI, or CT perfusion and xenon-CT can help in assessing brain oxygenation. However, transferring the patient requires cumbersome logistics. And after this exercise, we obtain merely a snapshot of the cerebral dynamics, not continuous data. This greatly limits their utility. Cerebral blood flow over large areas of the brain can be estimated by TCD, but operator variability limits their use.[1,3,18]

Invasive probes like the implanted brain tissue oxygen tension ($PbtO_2$) sensor also estimate CBF, but only over small regions.[18] The $PbtO_2$ is the product of CBF and cerebral arteriovenous oxygen tension difference.[71] Before implantation, the region at high risk for ischemia is determined by CT or MRI perfusion studies. Then a microcatheter is inserted in the white matter.[72] Despite being invasive, $PbtO_2$ monitors show low rates of complications. Depth of the probe and its nearness to the area of primary injury are crucial to the normal values of $PbtO_2$. Therefore, a CT verification of placement is important.[1] Besides placement, other factors that affect $PbtO_2$ include CPP, hemoglobin concentration, oxygen saturation, metabolic rate, and cerebral vasospasm.[73] $PbtO_2$ is an adjunctive along with ICP monitoring for CPP management.[71]

Normal $PbtO_2$ ranges from 25 to 50 mm Hg. In the clinical setting, moderate brain ischemia, critical brain ischemia, severe brain ischemia, and cell death are represented by $PbtO_2$ values of 15–25, <15, <10, and <5, respectively.[74] $PbtO_2$ <20 mm Hg is the recommended threshold to consider intervention.[38]

Regional Cerebral Flowmetry

Flowmetry sensors provide data on perfusion and tissue extraction. A laser doppler flowmeter measures erythrocyte flux.[1] It can monitor CBF continuously in TBI.[75] Currently, it remains a research tool as normal values in various physiological conditions have not been defined.[1] Thermal diffusion flowmetry (TDF) is an invasive, quantitative method with a high temporal resolution for continuous monitoring of CBF. This can avert an SBI as there is a therapeutic window for intervention.[76] A solid-state probe with proximal and distal thermistors combined with a distal heating element comprise the TDF. Probe placement is recommended in the white matter of the vascular territory, which is potentially at risk for vasospasm.[77] The probe has been used safely in patients with TBI and allows for assessment of autoregulation.[78] However, limitations to its use are device sensitive to positioning and its ability to measure only a very small volume. Currently, its impact on treatment to validate regular clinical use is lacking.[1] However, xenon perfusion CT has validated TDF. A CBF level below 15 mL/100 g/minute can reliably diagnose symptomatic vasospasm.[77]

Near-infrared Spectroscopy

Near-infrared spectroscopy observes real-time changes in regional cerebral oxygenation and provides information on desaturation. It is a bedside, noninvasive technique.[79] The depth of light penetration, hair follicle density, skin tone, and skull thickness influence the spatial resolution.[1] Near-infrared spectroscopy, when combined with systemic blood pressure and ICP monitors, can potentially assess cerebral autoregulation.[80] In one study in TBI cases, NIRS detected 97% of desaturations, whereas jugular venous oximetry detected only 53%.[81] Routine NIRS monitoring is currently not recommended in adult TBI patients due to lack of strong evidence.[82] Table 3 summarizes the recommendations as per the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care, which are endorsed by the American Academy of Neurology in 2018.[10]

Table 3: Summarized recommendations of the international multidisciplinary consensus conference on multimodality monitoring in neurocritical care[10]

Technology	*Indication*	*Recommendation*	*Quality of evidence*	*Prevalence in clinical practice*
ICP monitors	Patients with acute brain injury who are at risk of elevated intracranial pressure based on clinical or imaging features	Strong	Moderate	High
	Patients with imminent brain herniation to guide therapy	Strong	High	High
Cerebral autoregulation	Targeting of CPP management goals and prognostication in acute brain injury; pressure reactivity has been commonly used for this purpose, but many different approaches may be equally valid	Weak	Moderate	Emerging
Electroencephalography	Patients with persistent and unexplained alteration of mental status; convulsive status epilepticus that does not return to baseline within 60 minutes of treatment; refractory status epilepticus; comatose patients after cardiac arrest during therapeutic hypothermia and within 24 hours of rewarming	Strong	Low	High
	Patients with aneurysmal subarachnoid hemorrhage who have unreliable neurologic examination, at risk for delayed cerebral ischemia	Weak	Low	Low
Jugular venous bulb oximetry	Patients with or at risk for cerebral ischemia and/or hypoxia	Strong	Low	Low
Brain tissue oxygen monitoring	Patients with or at risk for cerebral ischemia and/or hypoxia	Strong	Low	Emerging
Cerebral microdialysis	Patients with or at risk of cerebral ischemia, hypoxia, energy failure, and glucose deprivation	Strong	Low	Low
Thermal diffusion flowmeter	Patients with risk of focal cerebral ischemia	Weak	Low	Low

Clinical Informatics Integration

Data from individual sensors present an incomplete assessment of patient physiology. We need systems that can integrate real-time MMM data with clinical data, laboratory values, imaging results, and medical record documentation.[83] This will set up a patient-specific "injury profile" to formulate an optimal treatment plan. Data must be clinically relevant and user-friendly.[7] Currently, the only commercially available system is the CNS monitor (Moberg Research). It allows the real-time monitoring of a single patient.[3]

Paradox

The "Best Trip Trial" was conducted on patients with severe traumatic brain injury. It evaluated treatment outcomes in two groups, one based on intraparenchymal ICP monitoring and other on clinical examination and imaging. The primary outcome of survival time, impaired consciousness and functional status at 3 and 6 months, and neuropsychological status at 6 months among the two groups was not significantly different. Treatment based on ICP monitoring was not superior to neurologic examination and serial neuroimaging for short-term or long-term recovery in severe TBI. Thus, the value of clinical examination cannot be stressed enough.[84]

The ongoing BOOST-2 trial is comparing the treatment of TBI based on ICP monitoring only vs ICP and brain tissue oxygenation monitoring. The results are expected to shed light on the effectiveness of MMM.[85]

Intraoperative MMM in spinal surgeries is believed to be worthwhile as it may avert the development of postoperative paraplegia, quadriplegia. Although its cost-effectiveness has yet not been quantified, the cost of MMM does not exceed the cost of prolonged health care for the neurological sequel. Well-designed trials, greater experience with MMM, and feedback from patients will adequately answer the question of cost-effectiveness.[86]

Future Direction and Conclusion

A recent telemedicine consensus statement recommended that the presence of an on-site full-time or part-time intensivist was the most efficient first step toward improving critical care quality.[87] Telemedicine intensive care recruits videoconferencing technology telemetry and the electronic medical record. This ensures that the distance between the patient and the caregiver is bridged.[88,89] Investment in information technology architecture, which can present the enormous data from MMM concisely, is necessary. Breakthroughs in the reliability of ocular ultrasound for detection of optic nerve sheath diameter[90] and pupillometry[91] are eagerly awaited. Currently, MMM-guided therapy improves physiologic neurologic variables but shows no demonstrable improvement in outcomes.[1,3,6,7,18,92]

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