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Traumatic brain injury (TBI) is a major cause of death and disability in the United States. The CDC estimates that 190 Americans died per day in 2021 from TBI-related injury and there were more than 214,000 hospitalizations related to TBI in 2020.1 Brain injury can be temporary or may result in severe and permanent disability or death and is typically classified as primary or secondary brain injury. Primary brain injury involves damage to the brain via transfer of kinetic energy and refers to damage immediately at the time of the incident and secondary brain injury evolves after the original injury and is due to factors such as hypoxemia, hypotension, high or low blood sugar, or seizures, among other potential causes.2 Brain injuries are often managed via medication, surgery, or exercise and therapies. Management depends heavily on the type of brain injury and its severity. For example, for brain injury associated with increased intracranial pressure, osmotic agents such as mannitol or active pharmaceutical ingredients (APIs) to decrease fluid around the brain may be administered along with other medications potentially including analgesics or anticonvulsants.3 Despite these treatment options, the Agency for Healthcare Research and Quality still reports longer stays and increased hospital mortality for patients diagnosed with TBI compared with other inpatient stays.4 Given the frequency and severity of brain injury in general and TBI specifically, development of new effective therapeutic options is crucial to reducing morbidity and mortality in patients suffering from brain injury. In this blog post, we evaluate recent literature regarding the usage of methylene blue for attenuation of adverse effects related to TBI and other brain injuries.

Methylene blue is commercially available as an injectable that has been FDA approved to treat cyanide poisoning, carbon monoxide poisoning, and methemoglobinemia. In recent years studies have begun to evaluate the potential benefit of methylene blue off label for a variety of conditions, including those associated with cognitive dysfunction such as Alzheimer's Disease, Parkinson's Disease, and brain injuries. Methylene

Blue is thought to have benefit for these conditions via its stabilizing effect on mitochondrial function and its effect on reduction of reactive oxygen species. Mitochondrial dysfunction and oxidative stress are often implicated in progressive neurodegenerative disorders such Alzheimer's disease and Parkinson's disease and in damage secondary to TBI.5,6 Additionally, new research both in vitro and in mice has suggests that methylene blue may reduce neuronal apoptosis and improve blood-brain barrier integrity.7

One randomized, blinded, placebo-controlled trial evaluated the effects of methylene blue 10mg/kg administered intraperitonially to mice and rats immediately or 24 hours post ischemic stroke. The study looked for both morphological changes as well as behavioral changes and found methylene blue to significantly alleviate brain injury both if administered immediately after brain injury and if administered 24 hours after the injury.8 Another randomized, double-blinded, vehicle-controlled trial evaluated oral methylene blue 4mg/kg for 21 days concluded that long term oral administration of low dose methylene blue reduced brain lesion volume and white matter damage after stroke induction in rats. The study noted functional behavioral benefit starting on day 7 and up to the full 60 days duration of the study.9

Another randomized blinded placebo-controlled trial in mice administered methylene blue 1mg/kg one hour post TBI and 0.5mg/kg three hours post TBI and evaluated the mice via behavioral assessments and MRI over the following 14 days. Methylene blue treated mice showed significantly decreased lesion volume vs the placebo group at all time points. Evaluators also saw a reduction in behavioral deficit in the treated group.10 In addition to studies evaluating benefit of acute administration, there are studies that have found benefit of methylene blue administration for months after brain injury as well. One study compared methylene blue in a single dose of 1mg/kg 30 minutes after injury to administration of that same dose 30 minutes after injury and then once monthly for a total of 6 months. The study noted repeated administration of methylene blue was the most effective for preservation of limb function.11

Though high quality randomized controlled trials are not yet available, methylene blue has also captured interest as a potential therapy for amelioration of post viral infection neurocognitive impairment and brain injury. Its potential benefit has been posited due to its effect on improving mitochondrial function and the benefit seen as a neuroprotective agent in other clinical situations such as ischemic stroke, neurodegenerative diseases, and chemotherapy-induced encephalopathy.13 The authors of one article posited 2-3mg/kg/day divided into three doses for 7-10 days for newly infected patients could be a reasonable dose for initial studies.14 Given one meta-analysis reported that 12-35% of patients with long COVID suffered from cognitive impairment (colloquially called "brain fog") and another found elevated brain injury markers during the acute phase of COVID-19, potential treatment and management strategies are in demand.13,14,15 Currently there are some trials evaluating the use of methylene blue for COVID-19, though, results and outcomes are not yet available.16,17

Brain injury and traumatic brain injury continue to be significant sources of morbidity and mortality and effective treatment options for prevention of acute and long-term damage are needed. Though in vitro data and in vivo animal data thus far is promising, more information and human trials are needed to evaluate the potential role of methylene blue as a treatment for acute and chronic brain injuries. For further questions on methylene blue and currently available data, feel free to reach out to the FACTS team at FACTS.support@fagronacademy.us

References:

1. Traumatic Brain Injury & Concussion. Centers for Disease Control and Prevention. https://www.cdc.gov/traumaticbraininjury/index.html. Updates 09/7/2023. Accessed 1/18/2024.
2. Dash HH, Chavali S. Management of traumatic brain injury patients. Korean J Anesthesiol. 2018 Feb;71(1):12-21. doi: 10.4097/kjae.2018.71.1.12. Epub 2018 Feb 1. PMID: 29441170; PMCID: PMC5809702.

3. Jha S, Ghewade P. Management and Treatment of Traumatic Brain Injuries. Cureus. 2022 Oct 23;14(10):e30617. doi: 10.7759/cureus.30617. PMID: 36426314; PMCID: PMC9681696.
4. New Data: Hospitalizations and Emergency Department Visits for Traumatic Brain Injury. Agency for Healthcare Research and Quality. New Data: Hospitalizations and Emergency Department Visits for Traumatic Brain Injury | Agency for Healthcare Research and Quality (ahrq.gov). Updated April 2020. Accessed February 13th 2024.
5. Seitkazina A, Yang JK, Kim S. Clinical effectiveness and prospects of methylene blue: a systematic review. Precision and Future Medicine. 2022; 6(4). https://doi.org/10.23838/pfm.2022.00079
6. Dash HH, Chavali S. Management of traumatic brain injury patients. Korean J Anesthesiol. 2018 Feb;71(1):12-21. doi: 10.4097/kjae.2018.71.1.12. Epub 2018 Feb 1. PMID: 29441170; PMCID: PMC5809702.
7. Shen J, Xin W, Li Q, Gao Y, Yuan L, Zhang J. Methylene blue reduces neuronal apoptosis and improves blood-brain barrier integrity after traumatic brain injury. Frontiers in Neurology. 2019: 10. https://doi.org/10.3389/fneur.2019.01133
8. Cheng Q, Chen X, Ma J et al. Effect of methylene blue on white matter injury after ischemic stroke. Oxidative Medicine and Cellular Longevity. 2021. https://doi.org/10.1155/2021/6632411
9. Huang L, Lu J, Cerqueira B, Liu Y, Jiang Z, Duong T. Chronic oral methylene blue treatment in a rat model of focal cerebral ischemia/reperfusion. Brain Research. 2018; 1678: 332-329.
10. Talley Watts L, Long JA, Chemello J, Van Koughnet S, Fernandez A, Huang S, Shen Q, Duong TQ. Methylene blue is neuroprotective against mild traumatic brain injury. J Neurotrauma. 2014 Jun 1;31(11):1063-71. doi: 10.1089/neu.2013.3193. Epub 2014 Apr 8. PMID: 24479842; PMCID: PMC4043255.
11. Genrikhs EE, Stelmashook EV, Voronkov DN, Novikova SV, Alexandrova OP, Gulyaev MV, Isaev NK. The Delayed Neuroprotective Effect of Methylene Blue in Experimental Rat Brain Trauma. Antioxidants. 2020; 9(5):377. https://doi.org/10.3390/antiox9050377
12. Magoon R, Bansal N, Singh A, Kashav R. Methylene blue: Subduing the post COVID-19 blues!. Med Hypotheses. 2021;150:110574. doi:10.1016/j.mehy.2021.110574
13. Yelin D, Moschopoulos C, Margalit I et al. ESCMID rapid guidelines for assessment and management of long COVID. Clinical Microbiology and Infection. 2022; 28(7): 955-972.
14. Scigliano G, Scigliano GA. Methylene blue in COVID-19. Medical Hypotheses. 2021; 146: 110455. https://doi.org/10.1016/j.mehy.2020.110455
15. Michael, B.D., Dunai, C., Needham, E.J. et al. Para-infectious brain injury in COVID-19 persists at follow-up despite attenuated cytokine and autoantibody responses. Nat Commun 14, 8487 (2023). https://doi.org/10.1038/s41467-023-42320-4
16. Ticino F. Methylene Blue Treatment of COVID-19. ClinicalTrials.gov identifier: NCT04635605. Updated April 20, 2022. Accessed January 29th, 2024. https://clinicaltrials.gov/study/NCT04635605
17. Alamdari D. Clinical Application of Methylene Blue for Treatment of COVID-19 Patients (COVID-19). ClinicalTrials.gov Identifier: NCT04370288. Updated May 4, 2020. Accessed January 29th, 2024. Clinical Application of Methylene Blue for Treatment of Covid-19 Patients - Full Text View - ClinicalTrials.gov

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