Defense and Veterans Brain Injury Center "Clinical Updates in Brain Injury Science Today [CUBIST]" Podcast
"Effect of Memantine on Serum Levels of Neuron-Specific Enolase and on the Glasgow Coma Scale in Patients With Moderate Traumatic Brain Injury"
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Host: Dr. Don Marion, MD

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Episode 111: Effect of Memantine on Moderate TBI

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Marion: Hi! Welcome to Clinical Updates in Brain Injury Science Today, or CUBIST, a podcast for health care providers about current research on traumatic brain injury, also known as TBI. This program is produced by the Defense and Veterans Brain Injury Center, otherwise known as DVBIC. I'm your host today, Don Marion. I'm a neurosurgeon and senior clinical consultant at DVBIC.

In today's episode, I'll be talking with Dr. Anne Bunner. Dr. Bunner is a biologist and program analyst here at DVBIC. Anne and I will discuss a study entitled: Effect of Memantine on Serum Levels of Neuron-Specific Enolase and on the Glasgow Coma Scale Score in Patients with Moderate Traumatic Brain Injury. This article was recently published in The Journal of Clinical Pharmacology by Mokhtari and colleagues.

Marion: Hi Anne, how are you?

Anne Bunner: Hi Don, I'm well, thanks!

Marion: Anne, what was the objective of this study?

Bunner: Doctors don't have effective drugs to treat moderate and severe TBI to prevent secondary brain injury and improve long-term outcomes. The goal here was to take a drug known for treating

Alzheimer's, which may have some neuroprotective effects, and see if it could improve short-term neurological function.

Marion: What were the key findings of this study?

Bunner: This was a randomized controlled trial of the Alzheimer's drug memantine, that showed little to no benefit with a seven day course for acute moderate TBI. Specifically, the author's found a trend towards improved Glasgow Coma Scale scores in the memantine group, but the difference in scores was only significant on the third day after injury. A serum biomarker of neuronal damage was lower in the memantine group at days three and seven.

Marion: Who were the participants, Anne?

Bunner: These were moderate TBI patients recruited from a trauma center in Iran. They were 95% male, 85% had been injured in motor vehicle accidents. Their mean age was about 30, and their mean Glasgow Coma Scale score was about 10. There were 19 participants randomized to the control group receiving standard care and 22 in the memantine group.

Marion: Not really a very large study, I guess.

Bunner: That's correct.

Marion: How were these folks assessed, Anne?

Bunner: Glasgow Coma Scale Score was assessed every day for seven days. Serum levels of neuron-specific enolase were measured at days one, three, and seven after injury. Neuron-specific enolase, or NSE, is present at high concentrations in neurons and leaks into the blood after TBI.

Marion: Anne, I'm a little bit confused. I know there are several serum biomarkers that have been evaluated for TBI, the most common are UCH-L1 and GFAP. Why did these authors choose NSE?

Bunner: That's a good question, Don. The authors didn't explain why they chose NSE over other serum biomarkers. In general, serum biomarkers differ in terms of the time scale of their rise and fall after injury and also in terms of the time point when their levels are most predictive of outcomes. The authors may have chosen NSE because it tends to remain elevated in blood for longer periods of time than UCH-L1 and GFAP and they wanted an outcome that would be useful at seven days post injury.

Marion: I see. The only time after injury when the treated group had a significantly better GCS was at three days. By seven days, there was no significant treatment effect. Please comment if you will on what this means in terms of long term benefit of the drug and the value of NSE as a surrogate for a treatment effect?

Bunner: These data don't tell us much about what to expect in these patients six months after injury. They do suggest the benefits of memantine after TBI are modest and short-lived. Glasgow Coma Scale is a functional measure that assesses awareness and neuron specific enolase is a surrogate measurement

for neuronal damage. In this case, the functional measure didn't match up with the surrogate measurement which calls into question whether NSE is a good predictor of TBI outcomes, or as you mentioned, a good surrogate for treatment effect. I think it's important to be careful and not to put too much stock into these quick and easy proxy measurements that may or may not be predictive of more meaningful clinical outcomes. I'll note that some other studies of NSE as a serum biomarker for TBI seem to suggest that it has limited usefulness for prognosis.

Marion: You know Anne, I completely agree. I think it's very tempting for investigators to want to find that upfront surrogate biomarker that will explain outcomes at six months or a year or 10 years down the road. We really have to be very careful and this study is an example of why.

What are some of the other limitations to this study?

Bunner: As I mentioned, this was just seven days, with no long-term follow-up. Of course with moderate TBI, we do want to know how patients are going to be doing six or 12 months down the line. It was a relatively small sample as you noted, just 41 patients total. It was not blinded, so the controlled participants where not receiving a placebo. Also, the results included little or no information about CT scan findings, which is concerning because we know that hematomas and intracranial hemorrhage have large effects on TBI outcomes. Finally, as mentioned above, NSE may or may not be a meaningful surrogate for brain damage and recovery.

Marion: What is your takeaway then, Anne?

Bunner: These results are modest but interesting. Future studies will hopefully reveal whether and which patients might benefit from memantine administration.

Marion: Thank you so much Anne for your insights. That's all we have time for today. We hope you enjoyed this quick literature update.

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CUBIST is produced and edited by Deborah Bailin and was hosted today by me, Don Marion. It is a product of the Defense and Veteran's Brain Injury Center, led by acting division head Kathy Helmick. Thank you for listening. In our next episode we will explore recent concussion literature.

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