NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 6 – Neuroprotection

Methylprednisolone: A Case Study in Neuroprotection Research

Methylprednisolone has been studied in large clinical trials over a period of decades, but there is still controversy over whether or how it should be used to treat people with an SCI. The controversy illustrates the challenges with studying SCI therapies, and also shows how important it is for SCI research advocates to have a role in designing, interpreting, and disseminating research results.

The trials enrolled people with acute SCI, which is challenging to study for several reasons. The first reason is that when it comes to neuroprotection, time is of the essence. We know from preclinical experiments that neuroprotection therapies work best in animals when given soon after injury. Scientists don't have a precise way to translate the time between injury and treatment in animal models to an equivalent time point in humans. And in most cases, it isn't possible to treat a person who sustains an SCI right away. They may first need to be transported to a hospital or trauma center, and they will then need to be evaluated before treatment can start.

Another complicating factor is that spinal shock after a traumatic SCI can make the initial assessment of neurological function difficult, which in turn makes it difficult to ascertain improvement. What may initially look like a complete loss of sensation and movement below the injury can improve over the days to weeks following the injury.

In addition, over time, some people with an SCI regain some motor and sensory function even without treatment. In a clinical trial in acute SCI, that can make it difficult to tell whether improvements that participants experience are due to treatment or would have happened anyway. Some people can even have a spontaneous improvement that is so large that no treatment benefit can be detected (this phenomenon is sometimes called a "ceiling effect")

The first clinical trial of methylprednisolone to treat SCI began in 1979, when steroids approved for other conditions were already widely used for acute SCI, and clinical trial methodology and reporting standards were not as well developed as they are today. The National Acute Spinal Cord Injury Study, now known as NASCIS 1, had no placebo group, but instead compared two different doses of methylprednisolone.

NASCIS 1 showed no relationship between dose and efficacy, which cast doubt on the benefit of using the steroid. The trial did show a small increase in wound infections in the higher-dose group. Doubt about efficacy and concerns about safety, combined with new preclinical

evidence suggesting even the high dose was insufficient, set the stage for a new placebo-controlled study called NASCIS 2.

In 1990, the investigators in NASCIS 2 reported an improvement in motor and sensory scores in people who were treated with methylprednisolone within 8 hours of an SCI. Methylprednisolone was quickly recommended as the standard of care for acute SCI, with two consequences for subsequent research:

First, the accepted evidence that methylprednisolone was effective made it unethical to conduct a randomized, placebo-controlled trial to confirm the results of NASCIS 2. Second, clinical trials and preclinical studies of other therapies for acute SCI began to use methylprednisolone as a comparator.

Soon, the SCI research community began to raise questions about the NASCIS 2 results. For example: Were the reported improvements due to chance? The trial did not meet the prespecified primary endpoint, which measured neurological function in people treated within *twelve* hours of injury, not eight. Therefore none of the study's other results could be considered conclusive. In addition, the subgroup of people who were treated within 8 hours was much smaller than the total trial population.

Some researchers also wondered why, when, and how the investigators selected the 8-hour cut-off to report. It was not the primary endpoint, and the NASCIS 2 investigators did not explain why they chose it. They also did not report data for other timepoints that would allow comparisons.

Finally, critics of the study also asked whether the endpoints were valid, measured consistently, and appropriate for a study in acute SCI. The endpoints used to measure motor and sensory scores in NASCIS 2 were not well described, so it wasn't possible to tell whether they might have been used differently by different investigators.

In addition, the improvement in motor and sensory scores was small, and functional improvements were not measured, so it wasn't clear how meaningful the improvements might be to people with an SCI. Some of the people who were enrolled had normal motor and/or sensory function to start with, so they couldn't have shown any improvement on the endpoints that NASCIS 2 used.

Over the next few years, without placebo-controlled studies to test the efficacy of methylprednisolone, clinical trials increasingly highlighted adverse events. As a result, methylprednisolone was downgraded in medical guidelines from the standard of care to an "option" for treating acute SCI depending upon the timing of administration.

Today, some doctors still use methylprednisolone for acute SCI based on the clinical data suggesting a benefit, the lack of alternatives, and the ability to treat the most common adverse events, including infections and bleeding.

Key observations from this example include:

- The NASCIS 2 study design and the way it was reported made it difficult even for experts to interpret the data.
- The endpoints used in NASCIS 2 were not an appropriate way to evaluate all of the people who were enrolled in the study, because some people did not have the motor and sensory impairments the endpoints measured.
- It was unclear whether or how the endpoints used in NASCIS 2 would relate to improvements that are meaningful and important to people with SCI.
- The studies of methylprednisolone still have not answered how early it must be given to maximize an improvement in outcomes.
- None of the debate included input from people living with SCI about how much benefit is meaningful in daily life, how much risk was an acceptable trade-off for that benefit, and how to think through the trade-offs.