Neurospine 2021;18(1):17-19.
https://doi.org/10.14245/ns.2142234.117

Neurospine
pISSN 2586-6583 eISSN 2586-6591

Editorial

Commentary on "The Influence of Timing of Surgical Decompression for Acute Spinal Cord Injury: A Pooled Analysis of Individual Patient Data"

James David Guest[1], Steven Kirshblum[2]

[1]Miller School of Medicine, The University of Miami, Miami, FL, USA
[2]Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School, Newark, NJ, USA

Corresponding Author
James David Guest
https://orcid.org/0000-0003-0931-0286

Miller School of Medicine, The University of Miami, Miami, FL, USA
Email: jguest@med.miami.edu

This is a review of the study by Badhiwala et al.,[1] "The Influence of Timing of Surgical Decompression for Acute Spinal Cord Injury: A Pooled Analysis of Individual Patient Data" published in the *Lancet Neurology* Dec 21, 2020.

This study is important for informing practice due both to its content, conclusions, and state-of-the-art methodology. It further informs the question as to whether the timing of decompression surgery has a "neuroprotective" influence following spinal cord injury (SCI). In the study, modern meta-analytical techniques were utilized to analyze pooled harmonized data from 4 independent prospective multicenter data sources covering the years 1991 to 2017. The data sets capture acute to longer-term neurological outcomes following traumatic SCI and utilized the North American Clinical Trials registry,[2] STASCIS (Surgical Timing in Acute Spinal Cord Injury Study),[3] Sygen,[4] and National Acute Spinal Cord Injury Study (NASCIS) III.[5] The main variable assessed in this study was the impact of the timing of surgical decompression on neurological recovery. The authors were able to analyze pooled individual patient data (IPD) in aggregate from source material. The endpoint was the change in motor score from baseline to 1-year follow-up.

There are several novel aspects of this study including the large sample of aggregate data that consisted of 1,548 eligible patients. An important analysis technique that was utilized is the restricted cubic spline method. This method allows testing for a nonlinear association between the time to decompression and the change in motor score. Time was treated as a continuous variable and the proportions of the time bins also shown in Fig. 3 in the study. It is notable that the largest cohorts were in the 8- to 24-hour time to surgical decompression period frame even including data from the 1990s. Thus, in the included studies early decompression was more common than late. A steep nonlinear association was found that flattened out after 36 hours. This implies that earlier decompression times have more impact on outcome than later. One issue to bear in mind is that there can be inaccuracy in the very early ISNCSCI (International Standards for Neurological Classification of Spinal Cord Injury) exam.[6] This could lead to an overestimate of the effect if, for example, a person was scored as the American Spinal Cord Injury Association Impairment Scale (AIS) A on a very early exam (within 4 hours) initially.[7] As conversion (for example to an AIS B or C) from this early time period occurs at a high rate, this change might be interpreted as recov-

ery from the surgery but could also be due to natural conversion from an early exam or due to an inaccurate initial exam in the challenging very early period after SCI.

Another important data analysis issue was in performing a one-stage hierarchical mixed-effects regression that allowed the IPD to be assessed against the regression variables at once. The hierarchical methodology allowed the impact of the individual datasets that spanned a substantial time period to be examined. One problem that can arise in this IPD approach is that the aggregate data may take on statistical distribution properties that were not present in the original studies. This is often described as how the individual studies cluster for the outcome of interest and the observed variances. Nuances of studies, historical, and baseline differences can be "washed out" by these methods. To correct for this, there are 2 main approaches, a stratified or random intercept.[8]

We get some insight into the importance of this modeling from Table S4 that compares the baseline characteristics between the 4 data sources, where for example one sees the notable difference in the average age across the studies, and e.g., the fraction of cervical injury, influenced by the fact that STASCIS enrolled only cervically injured patients. The Forest plots for the odds ratios dichotomized to early and later surgery are shown in Fig. 2, where one can appreciate that there are some considerable differences between the studies, with a smaller effect of early surgery on total motor score and pin prick score in the NASCIS II and Sygen studies respectively.

The overall IPD meta-analysis variance is estimated by the inverse variance method to assign greater weight to larger studies. The contribution of the variables: age, mechanism-of-injury, AIS grade, spinal injury level, and administration of methylprednisolone was adjusted for as fixed effects covariates to allow the effect of the surgery time (early/late) to be estimated more accurately.

We are told that the datasets were harmonized but it's not clear if that presented challenges and what compromises were needed? As examples of limitations, the original endpoint of NASCIS III was at 6 months and not 1 year, and only 14 extremity muscles were assessed versus 20 as is the current standard.[5,9] In addition, the reported analysis used data from one side of the body only. There was no placebo control in NACIS III, only methylprednisolone and tirilazad were tested. Surgical decompression is not mentioned in the index report or for the 1-year follow-up, an indictor perhaps of the important changes in care perception across the 32 ensuing years. For the Sygen study,[4,10] all patients received methylprednisolone. The outcome assessment used the Modified Benzel scale that added stratification for the AIS D grade. The authors were thus reliant on the accuracy of reporting in case report forms especially for NASCIS III and Sygen where timing of decompression was not a key variable.

The problem with missing data is intrinsic to the exercise of meta-analysis. In this study, 2 adjustment methods were utilized, one was the last analysis carried forward, and the other was multiple imputation using a Markov chain analysis. Sensitivity analyses have the purpose to examine the robustness of the study findings if the methods are changed.[11] Three comparisons were made, 1 stage versus 2 stage for each key outcome, changing the method of data imputation, and eliminating data imputation altogether. None of the alterations to the analysis substantially changed the findings. However, the absence of 1-year data may generally reduce the maximal neurological recovery observed,[12] despite the use of imputation. In summary, the IPD study allowed a relationship of timing of surgery to neurological outcome to be assessed from multiple studies of importance in the SCI field, even though this variable was not initially reported from the NASCIS and Sygen studies. While some questions are raised regarding this analysis, important information can be gleaned, and the application of these advanced data analysis methods in the SCI field enhances the value of carefully collected data.

CONFLICT OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Badhiwala JH, Wilson JR, Witiw CD, et al. The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data. Lancet Neurol 2021;20:117-26.
2. Grossman RG, Toups EG, Frankowski RF, et al. North American Clinical Trials Network for the Treatment of Spinal Cord Injury: goals and progress. J Neurosurg Spine 2012 Sep;17(1 Suppl):6-10.
3. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One 2012;7:e32037.
4. Geisler FH, Coleman WP, Grieco G, et al. The Sygen multicenter acute spinal cord injury study. Spine (Phila Pa 1976)

 https://doi.org/10.14245/ns.2142234.117

2001;26(24 Suppl):S87-98.
5. Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA 1997;277:1597-604.
6. Kirshblum S, Snider B, Eren F, et al. Characterizing natural recovery after traumatic spinal cord injury. J Neurotrauma 2021 Jan 22 [Epub]. https://doi.org/10.1089/neu.2020.7473.
7. Evaniew N, Sharifi B, Waheed Z, et al. The influence of neurological examination timing within hours after acute traumatic spinal cord injuries: an observational study. Spinal Cord 2020;58:247-54.
8. Legha A, Riley RD, Ensor J, et al. Individual participant data meta-analysis of continuous outcomes: A comparison of approaches for specifying and estimating one-stage models. Stat Med 2018;37:4404-20.
9. Bracken MB, Shepard MJ, Holford TR, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg 1998;89:699-706.
10. Geisler FH, Coleman WP, Grieco G, et al. Measurements and recovery patterns in a multicenter study of acute spinal cord injury. Spine (Phila Pa 1976) 2001;26(24 Suppl):S68-86.
11. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol 2013;13:92.
12. Fawcett JW, Curt A, Steeves JD, et al. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord 2007;45:190-205.

Title: Blue Number 3.
Artist: James Guest
Year: 2011
Media: Oil on canvas
Artist's note: Creativity has non-verbal right brain elements that can be channeled. It is sometimes difficult to know when to stop as there is always a risk that the next brush stroke will overload the canvas. Overthinking an abstract painting can ruin it.