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"Traumatic Thoracic ASIA A Examinations and Potential for Clinical Trials"

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ABSTRACT

Study Design: Retrospective review of prospective database

Objectives: To define the variability of neurologic examination and recovery after non-penetrating complete thoracic spinal cord injuries (ASIA A).

Background Data: Neurologic examinations after SCI can be difficult and inconsistent. Unlike cervical SCI patients, alterations in thoracic (below T1) complete SCI (ASIA A – based on the ASIA Impairment Scale [AIS]) patients' exams are based only on sensory testing, thus changes in the neurological level (NL) are determined only by sensory changes.

Methods: A retrospective review of the placebo control patients in a multicenter prospective database utilized for the pharmacologic trial of Sygen. Patients were included if they had a complete thoracic SCI on initial evaluation, with completed ASIA examinations at follow-up weeks 4, 8, 16, 26 and 52. Specifically, pin prick (PP) and light touch (LT) were assessed and the absolute change was calculated as the number of spinal levels at a given observation time.

Results 3165 patients were initially screened for the Sygen clinical trial, of which 57 were the control placebo patients used in this analysis. Alterations from the baseline exam (PP and LT) were fairly consistent and the median change/recovery in neurologic examination was one spinal level. Across all observations post-baseline, the average change for PP was 1.48 +/- 0.13 (mean +/- SE), and for LT, 1.40 +/-0.13. There were equal proportions of directional changes (none, improved, lost).

Conclusions:

Changes in a thoracic complete (ASIA A) SCI patient ASIA examination as measured through sensory modalities (PP/LT) are fairly uncommon. The overall examination had only 1-2 level

variability across patients, indicating minimal change in the sensory exam over the follow-up period. Stability in the ASIA examination as measured through sensory modalities has thus been demonstrated over time, making it an excellent tool to monitor changes in neurologic function.

INTRODUCTION

Traumatic spinal cord injuries (SCI) are devastating events that typically affect a younger population, resulting in a significant loss of economic and social productivity. Determining the extent of injury and overall prognosis after a spinal cord injury is a complex process and is presently assessed through the neurologic examination. Unfortunately, in thoracic SCI patients the variability and consistency of these neurologic examinations are unknown, particularly due to the dependence on the sensory examination. Patients with injuries from T2-T10 are presently being targeted for pharmacologic and surgical interventions in future potential SCI therapies, because the distance between the last functioning motor units (T1 level) and the site of neurologic injury decreases their potential for losing motor function. The T10 cut off increases the chance of a pure spinal cord lesion, avoiding the conus medullaris and cauda equina.

The International Standards for Classification of Spinal Cord Injury (commonly known as the American Spinal Injury Association [ASIA] exam) examination is a validated neurologic evaluation tool utilized for baseline and serial examinations following spinal cord injury. [1, 2] This examination has been successfully utilized in multiple SCI trials [3-5]; however, its variability in isolated thoracic SCI is unknown. Unlike the cervical spinal cord injuries where the exact neurological level (NL) can be confirmed by the physical examination through both a motor and sensory level, the thoracic ASIA level (below T1) is defined by only the sensory portion of the examination. This article, therefore, analyzes a large population of complete thoracic SCI patients (ASIA A) to assess the variability of the thoracic ASIA examination.

METHODS

This is a retrospective review of the data obtained from the Sygen pharmaceutical trial for spinal cord injured patients specifically analyzing the placebo control patients who did not receive the study medication (Sygen). [6] The Sygen study was a prospective, double blind, randomized, stratified, multicenter trial of the influence of a GM1 ganglioside on neurologic recovery after SCI. Full details of the trial's design, recruitment and enrollment have been previously published. [6, 7] As part of the study, patients were excluded for the presence of: penetrating gunshot wounds, spinal cord transection, significant cauda equina, brachial or lumbosacral plexus, or peripheral nerve injury.

This particular analysis consisted of a retrospective review of the Sygen database to specifically analyze the variability of the ***thoracic*** ASIA examination and definition of the NL in complete motor and sensory spinal cord injury (ASIA A) patients. All examiners for Sygen were trained and reliability assessed. [6, 7] No patients had voluntary lower extremity movement, and were graded 0/5 out of a 6 grade point system. Sensory modalities, pin prick (PP) and light touch (LT), were assessed as the highest spinal level at which at least one dermatome (left or right) showed absent or abnormal response to stimulus. Thus the neurologic level of injury was the most caudal normally innervated dermatome. The complete ASIA examination including PP and LT levels was assessed at baseline (BAS) and at 4, 8, 16, 26 and 52 weeks. The absolute change in PP or LT was calculated as the number of spinal levels from baseline (up or down) at a given observation time. Averaging positive and negative changes (movement up and down the spinal cord) would actually be misleading, as positive and negative changes cancel each other out in calculation of the mean.

RESULTS

3165 patients were initially screened for inclusion into the prospective Sygen study, of which 797 acute spinal cord injuries (ASIA A) met the inclusion criteria and were successfully enrolled. This consisted of 516 cervical ASIA A patients, including 170 thoracic ASIA A patients. 138 of these 170 thoracic motor and sensory complete or ASIA A patients had documented ASIA examinations at: baseline (time of injury), 4 weeks, 8 weeks, 16 weeks, 26 weeks and 52 weeks post injury. However, only 135 of the 138 had completed sensory examinations consisting of both pin prick and light touch scores and thus were included in the final analysis. 51 were placebo control patients with injuries in the T2-T10 range (the analysis population for this article), separated by level in figure 1, tables 1 and 2.

Transitions or alterations from the baseline examination were fairly consistent for both PP and LT sensory modalities. The median movement was one spinal level in either a caudal or cranial direction, and 75% of patients were within two spinal levels. Across all observations post-baseline, the average movement for PP was 1.48 +/- 0.13 (mean +/- SE), and for LT, 1.40 +/-0.13.(tables 1 and 2) For weeks 4-26, the distribution of positional changes was approximately equal; at week 52, more than 70% of the sensory levels were at their baseline. The majority of measurements illustrated either no change from baseline or a shift of less than 3 levels. (figure 2)

DISCUSSION

There are approximately 10,000 spinal cord injury (SCI) patients annually in North America. [8] Attempts to maximize the potential for neurologic recovery after an acute SCI trauma have been fraught with numerous barriers. In recent years, fortunately, there have been significant advances through laboratory investigations in the understanding of the pathogenesis

and treatment of SCI. [9-13] However, when applied in clinical translational trials, these laboratory advances have not yielded the same clinical or therapeutic benefits. [5-7, 14-17] One difficulty clinically has been the limited ability to measure and interpret therapeutic effects of these treatment modalities.

In order to differentiate subtle clinical benefits afforded by pharmaceutical and translational clinical trials, we must have a comprehensive understanding of the natural history of the SCI disease process. This information will facilitate an accurate design of translational protocols and the ability to differentiate clinically significant findings. For example, patients with incomplete SCI (partial motor of sensory function below level of injury) have the greatest potential to spontaneously recover motor function. This variability of neurologic recovery will unduly influence clinical trials for acute SCI; trials will therefore likely require neurologically complete injuries (ASIA A) with their more consistent recovery pattern as well as for safety reasons.

The neurologic level (NL) of injury defined by the ASIA exam localizes functioning and injured motor neurons and sensory fibers in relation to the spinal cord anatomy. [1, 18] The ASIA examination has been validated in terms of its ability to quantify the degree of patient's neurologic injury as well as potential for further neurologic recovery. [19] Waters et al illustrated that the absence of sacral sparing of sensation is the most reliable and clinically useful definition of a complete spinal cord injury and is the premise of the ASIA A (complete) definition. [20] Thoracic ASIA A SCI patients, however, are the most difficult to clinically assess changes since their ASIA level has neither discrete anatomic landmarks nor concurrent motor nerve roots to verify the level.

Although the ASIA examination has been validated in SCI populations, there has been limited evaluation of the complete thoracic ASIA A SCI patients due to their small numbers. Savic et al performed a prospective observational study on the inter-rater reliability of motor and sensory examination performed according to the ASIA standards in 45 SCI patients. The authors concluded there was a very good level of agreement between examiners. [21] However, this study excluded patients whose ASIA level was defined based solely on sensation. (rostral to C4 or T2-L1) In this present analysis a large number of ASIA examinations on complete thoracic ASIA A patients (figure 1) were reviewed to assess the reliability of the examination in terms of its consistency during repeated evaluations through a one year period. Despite the numerous adverse influences on obtaining an accurate physical examination in thoracic ASIA A patients, we found the thoracic ASIA level of injury based on the sensory evaluation (T2-10) to be a very stable test to quantify and follow neurologic function. In fact, the median change of ASIA examination over this one year period was only a single thoracic spinal level in either a rostral or caudal direction. (Figures 3 and 4) Illustrated throughout this series was that not only were the patients' neurologic examinations stable, but also that there was no significant change in the patients' overall neurologic function for a one year period. Across all observations post-baseline, the average movement for pinprick (PP) was 1.48 +/- 0.13 (mean +/- SE), and for light-touch (LT), 1.40 +/-0.13. (Figure1) (mean +/- SE),

Furthermore, when analyzing the percentage of patients with neurologic change, both the pinprick and light touch sensations yielded similar results.(Figures 3 and 4) Approximately one third of patients either neurologically improved, worsened or remained the same within one thoracic spinal level (figure 4). The spontaneous recovery of only a single thoracic sensory level

can be correlated to the cervical SCI data, which shows that there is the potential for single level of return juxtaposed to the level of injury. [22-24]

Interestingly, the greatest variability in the thoracic ASIA A examination occurred during the first 4 week period after injury. This is most likely attributed to the early influence of surgical intervention (positive or negative), difficulty in precisely localizing the level due to a patient population in significant pain, sedation and being in an ICU setting.(Figure 2) However, examinations after the four week period illustrated remarkably similar and consistent results. This stabilization of the examination might be the result of the ability to obtain consistent neurologic assessments since the patient is in a more controlled environment. However, the multitude of consistent ASIA examinations further suggests that there is a plateau of neurologic recovery, thus inferring no further neurologic improvement after the four week period. Unfortunately, even the greatest degree of neurologic recovery occurred in only one third of the patients and was still only one thoracic spinal level. (figures 3,4) When analyzing the data by quartiles to view the degree of change in the ranges farthest from the median, even this variability was less than 5 segments and with time decreased significantly (fig 4 A and B)

Therefore, the ASIA examination identifies severely injured patients (ASIA A) who may benefit from inclusion in SCI clinical trials. The present study illustrates that thoracic (T2-10) ASIA A patients are excellent candidates for clinical trials in that the ASIA examination is stable enough to be sensitive to neurologic small changes. In addition, this patient group had limited spontaneous neurologic recovery during the one year follow-up period. Burns et al retrospectively reviewed the spontaneous motor recovery in 103 ASIA A patients at one year from injury and found similar results. Overall only 6.2% (5/81) of (ASIA A) converted to ASIA B status and no patient exhibited any motor recovery (ASIA C or D). [25] The authors concluded

that the ASIA examination at 48 hrs provides "a subset of patients with a negligible chance for motor recovery who would be suitable candidates for future clinical trials of invasive treatments." [25]

CONCLUSION

Changes in a thoracic complete (ASIA A) SCI patient examination as measured through sensory modalities (PP/LT) are fairly common in the first four weeks post-injury. However, the overall thoracic ASIA A examinations had only 1-2 level variability across patients over the one year follow-up period. Therefore, this is an excellent tool and patient population to monitor changes in neurologic function for potential SCI intervention.

Week	Caudal PP		No Change		Rostral PP	
	Mean	SE	Mean	SE	Mean	SE
4	35.85%	6.53%	33.96%	6.44%	30.19%	6.25%
8	34.00%	6.57%	32.00%	6.47%	34.00%	6.57%
16	32.69%	6.70%	30.77%	6.59%	36.54%	6.88%
26	38.78%	6.89%	40.82%	6.95%	20.41%	5.70%
52	12.96%	4.75%	74.07%	6.20%	12.96%	4.75%

Table I: distribution of directional changes over time (PP)

Week	Caudal LT		No Change		Rostral LT	
	Mean	SE	Mean	SE	Mean	SE
4	36.73%	6.82%	38.78%	6.89%	24.49%	6.08%
8	38.46%	6.88%	38.46%	6.88%	23.08%	5.96%
16	41.51%	6.77%	37.74%	6.66%	20.75%	5.57%
26	42.86%	6.86%	30.61%	6.39%	26.53%	6.12%
52	10.91%	4.45%	70.91%	6.49%	18.18%	5.51%

Table II: distribution of directional changes over time (LT)

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