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Patient Selection for Clinical Trials: The Reliability of the Early Spinal Cord Injury Examination

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ABSTRACT

Patients with incomplete spinal cord injuries can spontaneously recover motor function. Because of this, phase I and II trials of invasive interventions for acute spinal cord injury will likely involve neurologically complete injuries. It is therefore important to reliably identify complete injuries as early as possible. We examined the reliability of the early examination in motor complete spinal cord injuries by retrospectively analyzing the stability of baseline neurological status determined within 2 days of injury in 103 subjects. Baseline neurological status was compared to neurological status at follow-up, preferably within one week (101 of 103 subjects). When available ($n = 68$), neurological status at 1 year or later was also compared. Overall, 6.2% (5/81) of motor complete, sensory complete (ASIA A) subjects converted to motor complete, sensory incomplete status (ASIA B) between the initial and follow-up assessments; however, none exhibited motor recovery (ASIA C or D). At initial follow-up, 9.3% (4/43) of ASIA A subjects with factors affecting examination reliability were reclassified as ASIA B injuries compared to 2.6% (1/38) of ASIA A subjects without such factors. At year 1 or later, 6.7% (2/30) of ASIA A subjects without factors affecting exam reliability, converted to ASIA B status. None developed volitional motor function below the zone of injury. For subjects with factors affecting exam reliability, 17.4% (4/23) of ASIA A subjects converted to incomplete status and 13.0% (3/23) regained some motor function by one year or later (ASIA C or D). These data suggest that it is possible to identify within 48 h of injury, a subset of patients with a negligible chance for motor recovery who would be suitable candidates for future clinical trials of invasive treatments.

Key words: clinical trials; inclusion criteria; prognosis; spinal cord injury

INTRODUCTION

THE PAST DECADE has seen many advances in experimental spinal cord injury research. It is therefore anticipated that in the near future we will see an increased number of clinical trials evaluating new treatment strategies for acute spinal cord injury (SCI). To date, only three treatment strategies have been reported to ameliorate acute spinal cord injury, methylprednisolone, GM1-ganglioside, and thyrotropin-releasing hormone (Bracken et

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al., 1997, 1998, 1990; Geisler et al., 1991, 2001; Pitts et al., 1995).

One of the key challenges in translating basic science advances to the clinic is the proper selection of study subjects for phase I and II trials. This problem was identified as far back as 1994 by a National Institutes of Health (NIH) workshop convened to examine challenges to translational research (Reier et al., 1994). Proper selection of study subjects is particularly important for invasive procedures (e.g., cell transplantation, intrathecal administration of growth factors). In this setting, adverse events could compromise expected natural recovery. Because of this fact, it is relatively accepted that phase I trials of invasive therapies should be performed in individuals with complete injuries because of the well-documented poor prognosis of these patients and the improbability that an intervention will compromise spontaneous recovery (Burns and Ditunno, 2001; Kirshblum and O'Connor, 1998; Waters et al., 1992, 1993). In contrast, patients with incomplete injuries commonly experience substantial recovery.

In addition to the injury characteristics of the initial study population, the therapeutic window for the intended therapy will also be important. As evident in animal work, some interventions show greater promise when administered within the acute phase of injury (von Meyenburg et al., 1998). Extrapolating these experimental results to humans suggests that for some treatments, early intervention could be more effective than late intervention. It is because of the above issues that the early and accurate identification of complete injuries will be critical to phase I and II trials of invasive interventions where safety is still being established. The inadvertent inclusion of patients with incomplete injuries is clearly unacceptable as complications could adversely affect expected natural recovery. We therefore studied whether patients with clinically complete injuries and negligible potential for recovery can be accurately identified within 1–2 days of injury.

MATERIALS AND METHODS

Medical records of patients admitted to the Regional SCI Center of the Delaware Valley at Thomas Jefferson University with motor complete (ASIA A or B) SCIs from 1995 to 1997 were systematically reviewed. Patients with complete injuries were defined according to the criteria of the International Standards for Neurological and Functional Classification of Spinal Cord Injury and assigned as "ASIA A, ASIA B" according to the ASIA Impairment Scale contained therein (Maynard et al., 1997; American Spinal Injury Association, 1992) (Table 1). The definitions of ASIA A and B injuries were unchanged in the 1996 revision of the standards and therefore did not affect our patient categorization. ASIA A injuries have a complete conduction block as evidenced by the absence of detectable sensory or motor function in the lowest (sacral) segments of the spinal cord (Table 1). ASIA B subjects present with the absence of motor function ("complete paralysis") but some sensory preservation. They were therefore included in this study because of their interest to clinicians and for comparison to the ASIA A subjects.

In order to be included in the study cohort, subjects had to have a traumatic SCI, a baseline neurological examination within 48 h of injury, and an available follow-up examination prior to acute hospital discharge. Almost all of the follow-up examinations were performed within 1 week of the baseline examination (101 of 103 subjects). The follow-up examination within 1 week was examined in order to confirm the accuracy of the admission examination. In addition, when available ($n = 68$), neurological status from 1 year or later was recorded and analyzed. This time point was chosen because most recovery has occurred by one year, and consequently the consistency of the admission neurological status could be compared with long-term neurological status (Burns and Ditunno, 2001; Waters et al., 1992, 1993). Clinicians trained in the use of the ASIA criteria performed all assessments.

Table 1. ASIA Impairment Scale

A.	**Complete.** No motor or sensory function is preserved in the sacral segments S4–S5.
B.	**Sensory incomplete, motor complete.** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5.
C.	**Motor incomplete.** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
D.	**Motor incomplete.** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
E.	**Normal.** Motor and sensory function are normal.

There were 127 potential subjects and 103 patients met inclusion criteria.

Information from the initial, acute follow-up, and post 1-year neurologic examinations as well as subject age, gender, and injury etiology were recorded and entered into a database. Factors that were thought to have potentially impacted the reliability of examinations were also recorded. These included factors affecting cognition (traumatic brain injury, drug effects, and psychological disorders) or communication (ventilator dependency, language barrier). Such factors have previously been shown to decrease examination reliability (Maynard et al., 1979). Traumatic brain injury was defined by the presence of imaging abnormalities or a clinical diagnosis, based on the judgment of the involved physicians, documented in the medical record. Drug effects included intoxication with alcohol or illicit substances, chemical sedation/paralysis or administration of analgesics with documented impairment of cognition. Ventilator dependence at the time of initial assessment was also noted.

RESULTS

Table 2 summarizes subject demographics. The mean age of the study cohort was 36.2 years, and the median age was 30 years. The male-to-female ratio was 90:13. Fifty-two (50.5%) of the subjects had at least one factor that could have potentially decreased the reliability of the initial examination. The specific factors are outlined in Table 2.

Table 2. Patient Demographics

Mean age (n = 103)	36.2
Median age	30
Gender	
Male	90 (87.4%)
Female	13 (12.6%)
Etiology	
Fall	32 (31.1%)
MVA	29 (28.2%)
Firearm	28 (27.2%)
Sports	14 (13.6%)
Baseline evaluation	
Same day	79 (76.7%)
Within 1 day post-injury	23 (22.3%)
Within 2 days post-injury	1 (1.0%)
Interval from 1st to 2nd exam	
Same day	24 (23.3%)
1 day	42 (40.8%)
2 days	13 (12.6%)
3 days	15 (14.6%)
4 days	0 (0.0%)
5 days	5 (4.9%)
6 days	1 (1.0%)
7 days	1 (1.0%)
8 days	1 (1.0%)
21 days	1 (1.0%)

Table 3 summarizes the results. When the entire cohort is evaluated, only five of 81 (6.2%) subjects converted from complete (ASIA A) to incomplete status (ASIA B, C, D) at the time of the acute hospital follow-up examination. All of these subjects were reclassified as sensory incomplete, motor complete (ASIA B) subjects upon initial re-evaluation. Of the subjects whose status was initially motor complete, sensory incomplete (ASIA B), three of 22 (13.6%) subjects were reclassified as motor incomplete (ASIA C or D) at initial re-evaluation.

The study cohort was further divided into two subgroups: Group 1 (n = 52) included subjects with factors that could potentially diminish reliability at initial assessment and Group 2 (n = 51) consisted of subjects without such factors. Factors noted as possibly affecting reliability included closed head injury, drug effects, psychological disorders, ventilator dependency, and language barriers (Table 4). Of the sensory complete, motor complete (ASIA A) subjects, four of 43 (9.3%) in Group 1 converted to incomplete (ASIA B, C, D) status at follow-up assessment compared to one of 38 (2.6%) in Group 2. Although a higher rate was observed with Group 1, the difference did not reach statistical significance using Fisher's exact test (p = 0.36).

Follow-up data from 1 year or later were available for 68 subjects. Of the subjects (n = 53) classified as motor complete, sensory complete (ASIA A) within 48 h of injury, six of 53 (11.3%) were reclassified as incomplete (ASIA B, C, D) by 1 year or later with three of six having some volitional motor function. When analysis is limited to subjects without factors affecting reliability, two of 30 (6.7%) changed from complete to incomplete. Both subjects fell into the ASIA B category and had no motor function below the zone of injury. In comparison, for subjects with factors potentially affecting reliability, four of 23 (17.4%) converted from complete to incomplete. Three of these subjects developed volitional motor function (ASIA C or D) by 1 year. Again, a higher rate of conversion was observed for the unreliable group but statistical significance was not reached (p = 0.38). Of the motor complete, sensory incomplete (ASIA B) patients at initial assessment, nine of 15 (60.0%) subjects devel-

Table 3. ASIA Grade Conversion Rates

		ASIA grade at 1st exam (entire cohort)		*ASIA grade at 1st exam (reliable)*		*ASIA grade at 1st exam (unreliable)*	
		A (n = 81)	B (n = 22)	A (n = 38)	B (n = 13)	A (n = 43)	B (n = 9)
ASIA grade at 2nd exam	A	76	0	37	0	39	0
(n = 103)	B	5	19	1	10	4	9
	C	0	2	0	2	0	0
	D	0	1	0	1	0	0
		A (n = 53)	B (n = 15)	A (n = 30)	B (n = 10)	A (n = 23)	B (n = 5)
ASIA grade at 1 year	A	47	0	28	0	19	0
or later (n = 68)	B	3	6	2	4	1	2
	C	2	6	0	3	2	3
	D	1	3	0	3	1	0

oped volitional motor function (ASIA C or D) by 1 year or later.

DISCUSSION

Prior studies utilizing ASIA criteria have reported conversion rates of complete (ASIA A) to incomplete (ASIA B, C, D) status ranging from 4% to 13% (Marino et al., 1999; Waters et al., 1992, 1993). Our overall 1-year conversion rate of 11.3% was consistent with previous studies. The baseline examinations of two of these studies were performed later than 1 week post-injury, which would be expected to lower the conversion rate (Waters et al., 1992, 1993). The findings of these studies therefore cannot be used to select candidates for future interventions within the first week post-injury. Other studies utilized the Frankel scale, which predated the ASIA standards and thus had less precise definitions of incomplete and complete injuries (Frankel et al., 1969; Maynard et al., 1979; Waters et al., 1991). These imprecise definitions may account for the higher conversion rates found in these studies. For example, the study of Maynard et al., which included five patients presenting with head injuries, reported a conversion rate of approximately 19%. The conversion rate for Frankel's series of patients (123 complete) was approximately 34%.

Table 4. Factors Affecting Examination Reliability

Incidence of specific factors (%)	
No factors	51
Mechanical ventilation	47
Intoxication/sedation/paralysis	7
Closed head injury	5
Psychiatric illness	2
Language barrier	1
Severe pain	1
Cerebral palsy	1

Some subjects were affected by multiple factors.

Our study, based on the internationally accepted ASIA criteria, presents evidence that patients can be reliably identified as having complete (ASIA A) injuries within 24–48 h of admission and that these patients have a negligible chance of recovering meaningful motor function. When reassessed within 1 week, the ASIA impairment grade changed for only 6.2% (5/81) of ASIA A subjects. For patients without factors that initially diminished reliability, the ASIA impairment grade changed in only 2.6% (1/38) at re-assessment. In contrast, the ASIA impairment grade changed in 9.3% (4/43) of unreliable subjects. For subjects with 1 year or later follow-up, 6.7% (2/30) of the reliable subjects in contrast to 17.4% (4/23) of unreliable subjects, converted to incomplete status.

Although the above differences failed to reach statistical significance, we attribute this to small subject numbers. The conversion rates were higher for the unreliable group at both initial re-assessment and 1 year or later follow-up. Furthermore, three (3/23) of the unreliable group demonstrated some motor recovery at 1 year or later compared to none (0/30) of the reliable group.

The definition of a complete injury for this study and other referenced studies is based on clinical criteria rather than physiologic testing. Clinical determination of injury is more practical for application in large multi-center trials than physiologic assessment. An additional point is that in the setting of an unreliable sensory examination, the examiner will tend to downgrade or overestimate injury severity. For example, if sensory sparing could not be documented, a motor complete, sensory incomplete

(ASIA B) SCI could be mistakenly classified as a motor complete, sensory complete (ASIA A) SCI. Inadvertently enrolling and exposing ASIA B injuries to an invasive intervention might negatively impact on expected, natural recovery. In this study, 60% (9/15) of subjects with ASIA B injuries developed some volitional motor function by 1 year or later.

This information is critically important for future clinical trials that propose interventions within 1 week of injury. Early identification of subjects with negligible potential for recovery is particularly important for invasive interventions such as cell transplantation and intrathecal administration of growth factors. We conclude that, for reliable subjects, it can be established within 24–48 h that there is a negligible chance of motor recovery in patients with complete (ASIA A) injuries and therefore early interventions are highly unlikely to interfere with expected natural recovery. It is conceivable that such patients could be identified earlier; however, we are unable to draw such a conclusion given that baseline assessments for our subjects were performed within a window of 1–2 days of injury. These findings support the rationale for evaluating invasive treatments in subjects with ASIA A injuries during the first week post-injury.

This study also suggests that it is prudent to exclude from early treatment subjects with factors diminishing examination reliability such as closed head injury, drug effects, psychological disorders, ventilator dependence, and language barriers. Subjects who initially have motor complete injuries with some sensory sparing (ASIA B) should also be excluded, because the natural history of the injury often includes motor recovery. We found that 60% (9/15) of the ASIA B subjects with 1 year or later follow-up developed some motor recovery.

Another implication of this study is the need for examiners who will participate in clinical trials to be expertly trained (Cohen et al., 1994, 1996). All individuals who performed the evaluations utilized in our study had substantial experience applying the evaluation criteria of the American Spinal Injury Association. All of the findings of the present study, which is limited by its retrospective design, would be enhanced significantly by confirmation with appropriately designed prospective studies involving larger numbers of patients.

CONCLUSION

This study suggests that properly trained, skilled examiners can reliably identify within 24–48 h of injury, individuals with SCI who have a negligible chance of motor recovery. In order to accomplish this classification, it is important to exclude patients with factors that diminish examination reliability, such as closed head injury, drug effects, psychological disorders, ventilator dependence, and language barriers. It is also important that individuals performing evaluations be expertly trained in applying the evaluation criteria of the American Spinal Injury Association. These facts are particularly relevant for future clinical trials for acute SCI that propose interventions within the first week following injury. Finally, the retrospective evidence presented here would be strengthened by confirmation using a larger study with a prospective design.

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