Changes in electrical perceptual threshold in the first 6 months following spinal cord injury

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Objectives: To investigate the use of electrical perceptual threshold (EPT) testing to follow the natural history of sensory progression after complete and incomplete acute spinal cord injury (SCI) and to compare EPT changes with the American Spinal Injuries Association (ASIA) Impairment Scale (AIS).

Study Design: Prospective descriptive study.

Methods: ASIA examination and EPT testing was performed on 17 patients (7 AIS A, 10 AIS B–D), within 1, 3, and 6 months after acute SCI. EPT assessment was carried out bilaterally at ASIA sensory points from 2 levels above the neurological level to all levels below, including the sacral segments. Comparisons of EPT values above, at, and below the SCI were made at the three time points as well as comparisons of EPT data to ASIA assessment.

Results: There was poor agreement between lowest normal level on EPT and ASIA assessment. Over time, EPTs tended to deteriorate above and at the ASIA level in AIS A patients with modest changes below the neurological level of injury (NLI), mainly where EPTs correlated with the zone of partial preservation. Sacral sparing was detected in one patient with EPT testing, but not with ASIA assessment. AIS B–D patients showed improvement at the ASIA level and extensive changes, both improvement and deterioration, below the NLI.

Conclusion: EPT testing has sufficient sensitivity to detect subclinical changes in sensory function as early as the first month post-SCI, which is not apparent in ASIA examination. In particular, the testing is able to show abnormalities at and around the injury site for both complete and incomplete SCI. In addition, EPT allows for the detection and monitoring of alterations, both improvements and deterioration, in the abnormal range of sensation.

Keywords: American Spinal Injury Association Impairment Scale, Electrical perceptual threshold, Quantitative sensory testing, Sensory progression, Acute spinal cord injuries, Somatosensory-evoked potentials, Sensory dysfunction

Introduction

Measurement of sensory function and its progress following acute spinal cord injury (SCI) has been endorsed as an important marker of recovery for future clinical trials.^{1,2} Clinically, sensory function is assessed by the American Spinal Injury Association (ASIA) classification,³ which provides an overall ASIA Impairment Scale (AIS) score to describe the level and completeness of the injury, as well as sensory subscores for pinprick and light touch.

Electrical perceptual threshold (EPT) testing has been proposed and validated in recent years as a reliable semi-quantitative measure of sensory function.^{4–7} EPT testing is based on the activation of a variety of low threshold sensory nerve fibres⁸ and is sensitive to minor sensory impairments even in 'clinically normal' dermatomes above the neurological level of injury (NLI).⁹ It has

been shown that EPT testing is equal⁹ or superior^{7,8} to the ASIA in detecting subclinical sensory changes by assessing large diameter posterior column fibres. Furthermore, EPTs correlate well with somatosensory-evoked potentials (SSEPs) in the posterior cord⁸ and together may represent a more comprehensive picture of sensory dysfunction.

Our aim was to assess how EPT above and below the injury, including sacral dermatomes, change in the first 6 months after SCI and to compare this EPT progression with changes in the ASIA examination and associated AIS scores. To our knowledge, ours is the first study measuring sensory function across time points after acute SCI using EPT in ASIA dermatomes that include the sacral dermatomes.

Materials and methods

Participants

Seventeen volunteer patients (16 men and 1 woman; mean age (SD), 44.35 (20.6) years) with a diagnosis of

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complete or incomplete SCI as assessed by ASIA Impairment Scale^{3,10} participated in the study (Table 1). The cause of SCI was traumatic in all patients and the NLI varied from C3 to T12. Patients with a pre-existing history of peripheral neuropathy, skin disorders, systemic disease such as diabetes or renal failure or who were medically unstable were excluded from participation.

A control group of 45 healthy volunteers (29 females and 16 males, mean age (SD) 47.3 (16.5) and 40.4 (15.2) years, respectively) were used to provide reference values.¹¹

All subjects were recruited from an acute SCI unit within a large tertiary teaching hospital and provided written informed consent to participate. Approval for the study was given by the hospital's Human Research Ethics Committee. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Experimental design

All patients with acute SCI (of traumatic and non traumatic causation) admitted sequentially into the unit were invited to participate in the study as soon as they were deemed able to cooperate with an ASIA assessment and EPT testing. Patients underwent a clinical neurological assessment performed by an experienced spinal physician according to ASIA standards^{3,10} to determine neurological level and ASIA score. EPTs were measured by two trained assessors at ASIA dermatomes on both sides starting from 2 levels above the last normal neurological level as found on the ASIA

examination, down to the sacral segments S4/S5. EPT testing was conducted within 24 hours of ASIA assessment. The assessment time points were within the first month, 3 and 6 months post-injury. The first time points varied from 2 to 4 weeks (mean days $\pm$ (SD); $20.3 \pm (4.5)$), as some patients were in intensive care, or were unable to cooperate with an ASIA examination or extensive EPT early after injury; this first assessment will be referred to as the 1 month time point in the remainder of this paper.

Measurement protocol

Measurement of EPTs was performed as previously described in Leong *et al.*^{7,11}

Testing was conducted using a stimulator (DS7A, Digitimer Ltd) by using constant current square wave electrical pulses of 0.5 ms duration, 3-Hz stimulation frequency. Stimuli were delivered to the skin over ASIA sensory key points. The stimulus intensity was increased to a maximum current of 10 mA (milli-amperes). Subjects reported verbally when the first sensation was felt. This process was repeated 3 times on each dermatome and the lowest ascending stimulus intensity of the three trials was taken as the EPT value.

An EPT value was considered 'normal' if it was within 2SD of the mean for that dermatome in the gender-adjusted normogram,¹¹ 'abnormal' when it was $>2SD$ of the mean value. As in previous studies, at 10 mA the stimulation was stopped and a lack of response from the subject was noted as an 'absent' EPT value. This method has previously been employed to plot sensory dysfunction.^{6,12}

Table 1 Demographic data of the SCI volunteers

	Patient	Gender	Age	1 month ASIA	1 month EPT	6 months ASIA	6 months EPT
ASIA A (7)	A	M	55	C3 A	C2	C6 A*	C3*
	B	M	36	C3 A	C3	C3 A [‡]	C5*
	C	M	26	C4 A	C7	C7 A*	C7 [‡]
	D [§]	M	20	C5 A	C4	C5 B [‡]	C3 [‡]
	E	M	79	T2 A	T1	T1 A [‡]	T1 [‡]
	F	M	19	T10 A	T5	T11 A*	T10*
	G	M	40	T12 A	T12	T12 A [‡]	T11 [‡]
ASIA B–D (10)	H	M	45	C4 B	C4	C4 C [‡]	C5*
	I [§]	M	71	C4 C	C2	C4 C [‡]	C2 [‡]
	J	F	55	C4 D	C3	C3 D [‡]	C3 [‡]
	K	M	20	C5 C	C8	C8 D*	T1*
	L	M	68	C5 D	C5	C5 D [‡]	C5 [‡]
	M	M	81	C5 D	C3	C3 D [‡]	C4*
	N	M	16	C6 B	C8	C7 B*	T1*
	O	M	20	C6 D	C5	C6 D [‡]	T1*
	P	M	54	T11 D	L1	T10 D [‡]	L4*
	Q	M	36	T12 D	T12	L3 D*	L4*

*and [‡]Indicate an improvement or deterioration in level, respectively, at 6 months compared to 1 month, for the same test.

[‡]Indicates no change.

[§]Indicates the patients shown in Figs. 2 and 3.

Evaluation of EPTs

Comparisons of EPT values above, at, and below the SCI were made at the three time points (1, 3, and 6 months). In addition, EPT and ASIA levels were compared for each patient at each of the time points.

A change in the EPTs over time (ΔEPT) was calculated by comparing the EPT values at each of the time points. The difference in the EPT values was compared to the standard deviation occurring at that dermatome in a gender-adjusted, able-bodied population using the following formula:

$$\Delta\text{EPT} = [\text{EPT}^{\text{acute}} - \text{EPT}^{6\text{ months}}] / \text{SD}^{\text{dermatome}}$$

$$\begin{aligned} \text{i.e. } \Delta\text{EPT}^{\text{C5_Patient D}} &= 4.65 - 6.75 / 0.29 \\ &= -2.15 / 0.29 = -7.41 \end{aligned}$$

The ΔEPT reflects the change over time in relation to the range for a normal population for the same dermatome. The SD of able-bodied subjects¹¹ was used to allow for comparison, as the SCI sample size of $N = 17$ is too small to compute a reliable normogram.

EPT changes were assessed over the whole period (1–6 months) and subsequently for the first and second 3-month intervals separately. Due to asymmetries each side was treated as a separate EPT change.

As a lower EPT value means that the subject requires less current to elicit a sensation, EPTs should decrease with recovery. A positive ΔEPT , therefore, means an improvement in the sensory perception at that dermatome and a negative ΔEPT means a deterioration (i.e. as in the example). Although the minimal clinically significant difference for EPTs has yet to be elucidated, we propose that an EPT change of $>2\text{SD}$ for a dermatome can be reasonably considered to be a clinically significant change. The results are presented as per cent of dermatomes showing a specific change.

Statistical analysis

The software package Prism GraphPad 17.0 (Graphpad Software Inc., LaJolla, CA, USA) was used for all statistical comparisons.

Paired t -tests (two-tailed) were used to test for differences in demographic variables between patients with incomplete and complete injuries. Friedman's test was used to compare EPT changes at selected ASIA dermatomes over time.

Results

There was no statistical difference between the mean age of the groups of patients with complete and incomplete injuries ($P = 0.36$).

Changes in ASIA/AIS over time

The AIS score refers to the last level (at the ASIA dermatome) that is deemed neurologically intact and the severity of the resultant neurological impairment below this level, ranging from A to E.¹⁰

Of the seven patients scored as AIS A within 1 month post-SCI, one patient was reclassified to AIS B at 6 months (patient *D*). For the other AIS A patients, two remained stable over the 6 months, three patients improved (i.e. ASIA level shifted down), and one patient deteriorated (i.e. ASIA level shifted up) (Table 1).

Of the 10 patients scored as AIS B–D, two patients were reclassified to a better ASIA score at 6 months (patient *H*, B to C; patient *K*, C to D). In six patients, the ASIA level shifted over the 6 months: three patients improved and three patients deteriorated.

Changes in 'EPT level' over time

The 'EPT level' refers to the last level that has an EPT score within 2SD of the mean of that level taken from our gender-specific normogram.¹¹

Of the seven AIS A patients, a change in the EPT level occurred in five; in three patients the EPT level improved and in two patients it deteriorated. Of the 10 AIS B–D patients, 3 remained stable, an improvement in the EPT level occurred in 7 patients and no deterioration was noted.

Agreement between EPT and clinical ASIA

Of the seven AIS A patients at 1 month, the ASIA and EPT level agreed in two cases while four patients had EPT levels above the ASIA level and one patient had an EPT below the ASIA level. There were abnormal EPTs in 15 and 22% of cases at the ASIA level and 1 level above ASIA level, respectively. Below the ASIA level EPTs agreed well with the zone of partial preservation. At the sacral segments, one patient had pathological EPTs (patient *D*). By 6 months, only two patients' ASIA and EPT levels correlated, with four patients having EPT levels above the ASIA and one below.

Of the 10 AIS B–D patients at 1 month, the ASIA and EPT level agreed in three cases with four patients having EPT levels above the ASIA level and three patients below. There were abnormal EPTs in 45% of cases at ASIA level and 1 level above injury, respectively; 40 and 50% of dermatomes were significantly abnormal at 1 level and 5 levels below the injury, respectively. At the sacral segments, 40% were abnormal and 10% of dermatomes showed absence of EPTs. By 6 months, only two patients had the same EPT and ASIA level. Unlike AIS A cases, the number of patients with EPT

levels above the ASIA was only one, while the majority (seven cases) had EPT levels below the ASIA level.

In the whole cohort, ASIA and EPT levels were within one dermatome of each other in 10 patients at 1 month and 11 patients at 6 months.

Case illustrations

Fig. 1 illustrates EPT values for patient *D* – an AIS A patient (Table 1). Of note is the asymmetry around the ASIA level between the left and right side in terms of the last level with normal sensation as well as quantification of sensory impairment. This is typical of the entire cohort. Furthermore, there are abnormal EPTs

at C5, the ASIA level, above the clinical ASIA level, and in the sacral dermatomes. The latter correlated with a reclassification to ASIA B at 6 months.

The boxed insets show EPT values at the 1- and 6-month time points. EPTs increased at the ASIA level bilaterally, i.e. sensory perception deteriorated, with a moderate increase over the first 3 months and the majority of change occurring in the second 3 months. At 1 level above ASIA level, the EPT was stable on the right and increased on the left side, once again with the majority of increase occurring over the later 3-month period. EPTs were essentially stable 5 levels below the ASIA level with minimal changes occurring at the 3-month time point.

Figure 1 EPT data for patient *D* (AIS A, C4) at 1 month (dashed line) and 6 months (solid line) compared to male age-matched normogram from Leong *et al.*¹¹ (grey area shows the normogram mean +2SD). Boxed insets show the EPT values on the left and right sides at 1 and 6 months post-SCI at 1 level above ASIA (upper box), ASIA level (middle box), and 5 levels below (lower box).

Fig. 2 illustrates the EPT measurements of patient I – an AIS C patient. Of note are abnormal EPTs above and at the ASIA level, similar to the patient above. In addition, many changes occurred to the dermatomes below the ASIA level, not detected on the sensory subscores of the ASIA examination.

The boxed insets show that EPTs decreased bilaterally above the injury, a trend that commences at the 3-month time point. At the ASIA level, the right-hand side shows an increase and the left-hand side a decrease at 3 months, but both sides show an increase in EPT by 6 months. Five levels below the injury the EPT increases on both sides at the 3-month time point, but by 6

months EPTs have increased on the right and decreased on the left side.

Comparison of EPT changes at selected dermatomes over time

In order to compare changes in EPTs for our whole sample, we looked at the following five selected dermatomes: at the ASIA level, 1 level above, 1 level below, 5 levels below ASIA level and at the sacral dermatomes S4/S5 (Fig. 3).

Over the 6 months most AIS A patients showed clinically significant changes. Deterioration was the predominant trend at the ASIA level, occurring in 21% of

Figure 2 EPT recordings for patient I (C4 ASIA C) at 1 month (dashed line) and 6 months (solid line) compared to male age-matched normogram from Leong *et al.*¹¹ (grey area shows the normogram mean +2SD). Boxed insets show the EPT values on the left and right sides at 1 and 6 months post-SCI at 1 level above ASIA (upper box), ASIA level (middle box), and 5 levels below (lower box).

Figure 3 Changes in EPT (Δ EPT) over 6 months following acute SCI for complete (circle) and incomplete (diamond) patients at 1 level above, at ASIA level, 1 level below, 5 levels below, and at the sacral dermatomes S4/5. The grey area indicates the range of clinically insignificant change. Note that densely packed data points may appear less due to overlap.

dermatomes ($P = 0.12$) and 1 level above the injury in 57% of dermatomes ($P = 0.041$). At 1 level below the ASIA level, there was no clear trend in the sensory change (21% improving and deteriorating, respectively, $P = 0.558$). At 5 levels below the ASIA level, significant improvement was noted in 29% of dermatomes ($P = 0.046$). Improvement in the sacral dermatomes was only noted in one patient, but overall the lack of sensory perception remained ($P = 0.37$).

AIS B–D patients showed clinically significant improvement in 20% of cases at the ASIA level ($P = 0.052$). At 1 level above the injury, no clear trend was noted (10% deterioration and improvement, respectively; $P = 0.43$). At 1 level below the ASIA level, 25% improved and 15% deteriorated; at 5 levels below ASIA, 20% of dermatomes improved and 30% deteriorated, whereas in the sacral dermatomes 15% improved and deteriorated, respectively. Overall as a cohort there were changes in many dermatomes below the ASIA level; however, no clear trend was noted with P values 0.56 (1 level below injury), 0.43 (5 levels below the injury), and 0.94 (at the sacral level).

Timing of EPT changes

We further assessed the time course of EPT changes to determine whether these occurred in the first or subsequent 3-month periods (Fig. 4).

Results show that many AIS A patients had deteriorated on EPT testing at the ASIA level and 1 level above during the first 3 months, with 35 and 68% of dermatomes, respectively, deteriorating, while improvements were noted predominantly during the 3–6-month period with 35% improving. One level below the ASIA it was observed that 42% of dermatomes shifted during the first 3 months (both improving and deteriorating)

and only 7% in the 3–6-month period. At 5 levels below, 25% of dermatomes improved and 30% deteriorated. At the sacral dermatomes EPT changes were only noted for one patient who was reclassified.

In ASIA B–D patients no clear time trend was observed at the ASIA level, 1 level below ASIA, and the sacral dermatomes. Similar to AIS A patients, deterioration 1 level above the injury tended to occur early in 35% of dermatomes and deterioration later. At 5 levels below the injury, it was noted that 40% of dermatomes significantly improved and 25% deteriorated during the first 3 months and 35 and 50% of dermatomes changed, respectively, in the subsequent 3 months.

Discussion

Reliability of ASIA

Extensive research has gone into establishing the reliability and repeatability of the ASIA standards,^{6,13,14} with further improvements noted after revisions in 2000.¹⁴ It was noted however, that the sensory subscores carry poorer inter-rater reliability compared to the AIS score.^{13,15} Additionally, the reliability of ASIA assessment was questioned in the context of early assessment,^{16,17} incomplete injuries,¹³ and children under the age of 10 years.

Currently, the minimal clinically important difference of ASIA sensory subscores or indeed of AIS scores remains unknown.¹⁴ However, it appears that in longitudinal sensory examinations ASIA sensory scores fail to measure subtle segmental changes, which can infer a functional benefit to the patient.⁸ As such, it is recognized that electrophysiological measures have an important role in complementing the clinical assessment, as they are able to detect and quantify subclinical sensory changes.¹²

Completes

Incompletes

Figure 4 Time course of changes in EPT (Δ EPT) over the first 6 months following SCI; changes occurring from acute to 3 months (gray) vs. 3–6 months (black) for complete (circle, upper panel) and incomplete (diamond, lower panel) patients at 1 level above, at ASIA level, 1 level below, 5 levels below, and at the sacral dermatomes S4/5. The grey area indicates the range of clinically insignificant change. Note that densely packed data points may appear less due to overlap.

Natural progression

Sensory recovery is strongly linked to the completeness of the SCI¹⁸ with conversion rates of complete injuries (AIS A) reported from 10 to 30%^{16,19–21} as compared to much higher rates for incomplete injuries. Significant improvements tend to occur in the first 6 months post-injury,^{18,19} but may still be observed up to 5 years post-injury.²⁰ Although the ASIA examination is used to establish the NLI in the acute setting, it is known that examiners tend to over-estimate injuries, particularly if sacral sparing cannot be reliably established.¹⁶ This is thought to be the reason as to why lower conversion rates are noted if baseline ASIA examinations are performed 72 hours to 2 weeks post-injury,^{14,17} as compared to at admission.

EPT vs. ASIA

In this study, we recorded the baseline AIS at 2–4 weeks post-injury and within 24 hours of EPT measurement. Overall the agreement between EPT and ASIA level was modest (43% for AIS A and 30% AIS B–D)

within 1 month, with even greater discrepancy at 6 months. This may be due in part due to the asymmetry of injury and that EPTs assess posterior column function only. The injury level measured by EPT was typically several segments higher than the clinical estimate of the ASIA level, especially within the first month, suggesting that EPT testing is picking up subclinical deficits above the ASIA level. This observation is similar to previous reports from Savic *et al.* 2006 in patients at least 3 months post-injury. Previous electrophysiological studies have also found subclinical changes above the level of injury for different sensory modalities.^{4,22} This degree of sensitivity could be required to assess differences in sensory recovery, especially when improvements might be limited to 1 to 2 dermatomes adjacent to the ASIA level.

Prognostic value

The detection of subclinical changes could also be valuable in refining classification and prognostication. A patient who is AIS A but has detectable EPTs at the

sacral dermatomes may have a higher likelihood of conversion to AIS B than someone without, as in the case of patient D. EPT testing could be used to help determine classification in unclear cases, for example in patients who have ‘rectal sensation’ during bowel care, but do not have sacral sensation on ASIA testing. It has been demonstrated that sacral sensation is a major reason for conversion²¹ and as EPT measurements could add precision where early accurate scoring is critical, as in the context of interventional trials. Previous studies have shown that motor-evoked potentials and SSEPs have a strong prognostic value for functional outcome.^{23–27} A recent study by Kramer *et al.*²⁸ showed that dermatomal SSEP recordings were in fact often preceded by EPTs and showed variable correlation with concomitant recovery of EPT in 60% of cases at follow-up. However, to date no reliable long-term evaluation of prognosis exists for most QST including EPTs.^{2,27}

Mechanism

Both neural plasticity and neural repair mechanisms such as remyelination, revascularization, and reconnection are thought to be responsible for neuronal recovery following SCI.²⁹ It is, however, unclear as to what extent each of these mechanisms contribute to changes following complete and incomplete injury and what time course they follow.

Our study showed that overall AIS A patients tended to deteriorate at and above the level of injury and that deterioration occurred early on. These early changes may be attributable to some secondary injury mechanisms, such as inflammation, apoptosis, excitotoxicity, and glial degeneration in the penumbra adjacent to the primary injury,^{30,31} all of which occur days to weeks following acute SCI.

Below the injury more changes were noted during the first 3 months compared to the subsequent 3 months. A likely pathophysiological mechanism for the progressive decline in changes is that of demyelination and Wallerian degeneration, the process of progressive loss of transected axons that occurs weeks to months following the injury.³¹

AIS B–D patients had a similar picture above the lesion site albeit less dramatic. However, these patients showed significant changes occurring both at the level as well as below the injury, both improvements and deterioration without any obvious trends related to the time course, which might suggest that several processes are occurring simultaneously. Early recovery in incomplete injury is thought to be partly due to recovery of conduction block in descending axons, due to resorption

of cord oedema and haematomyelia.³² Additionally, a mechanism suggested for motor recovery in incomplete injury, which may be applicable to sensory recovery, is that of synaptic plasticity around the glial scar, which occurs during the months following SCI³³ and is promoted during rehabilitation.³¹

Study limitations

Developing a technique that allows quantification of sensory testing in the spinal cord population is inherently associated with limitations. Varying degrees of skin and electrode interference related to temperature, body hair, and amount of subcutaneous tissue were minimized by shaving patients, standardizing electrode placements as carefully as possible, and conducting the assessment in a temperature-regulated room. A cut-off point of 10 mA was used as the maximum stimulation intensity in this study and has been used throughout the literature for EPT testing.^{5,7,9} It was chosen to ensure that no tissue damage occurred in patients with absent sensory perception. This cut-off point might however account for some of the unexpected results. For example, the apparent ‘absence’ of sensory perception in 10% of the sacral dermatomes of AIS B–D patients, a group clinically defined as having intact sacral sensation. Furthermore, in this form of testing the ability of the patient to concentrate and promptly report a sensory stimulus is paramount. The assessment was discontinued if the patient felt tired or was too unwell to reliably participate. It is also the reason why change is assessed longitudinally.

Additionally, the data were compared to an able-bodied population sample as previously published.¹¹

Due to sample size limitation age-adjusted normograms could not be used, despite aging being a pertinent factor in the extent of natural recovery.³⁴

Overall it can be said that besides the limitations of the methodology itself, the inherent variability of a sample of patients with SCI, related to factors such as differences in injury mechanisms, level of injury, extent of tract damage, and associated injuries, would in part account for the wide variation in sensory perception seen between individuals in this sample.

Conclusion

Our results show that EPT testing can add resolution to the assessment of sensory function in acute SCI by detecting and quantifying subclinical changes at and near the ASIA level and in the sacral dermatomes. This is of particular importance in the context of early assessment as in the recruitment to clinical trials and monitoring of therapeutic intervention.

Further study is required to establish the value of EPT in predicting sensory progression and therefore allowing for EPT and other QST measurements to be used for prognostic evaluation alongside ASIA in the setting of acute SCI.

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