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# Prognosis in prolonged coma patients with diffuse axonal injury assessed by somatosensory evoked potential☆

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## Abstract

A total of 43 prolonged coma patients with diffuse axonal injury received the somatosensory evoked potential examination one month after injury in the First Affiliated Hospital, School of Medicine, Zhejiang University in China. Somatosensory evoked potentials were graded as normal, abnormal or absent (grades I–III) according to N20 amplitude and central conduction time. The outcome in patients with grade III somatosensory evoked potential was in each case unfavorable. The prognostic accuracy of grade III somatosensory evoked potential for unfavorable and non-awakening outcome was 100% and 80%, respectively. The prognostic accuracy of grade I somatosensory evoked potential for favorable and wakening outcome was 86% and 100%, respectively. These results suggest that somatosensory evoked potential grade is closely correlated with coma severity and degree of recovery. Somatosensory evoked potential is a valuable diagnostic tool to assess prognosis in prolonged coma patients with diffuse axonal injury.

## Key Words

neural regeneration; brain injury; somatosensory evoked potential; diffuse axonal injury; coma; prognosis; awakening; nerve electrophysiology; grants-supported paper; neuroregeneration

## Research Highlights

(1) This is the first application of somatosensory evoked potential for assessing prognosis of prolonged coma patients with diffuse axonal injury.
(2) The examination of somatosensory evoked potential 1 month after diffuse axonal injury could reduce the possibility of reappearance of cortical responses, resulting in a more reliable clinical evaluation.
(3) Somatosensory evoked potential was used not only to evaluate prognosis, but also to assess the accuracy of outcome prediction in prolonged coma patients with diffuse axonal injury.

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## INTRODUCTION

Diffuse axonal injury occurs in nearly half of all severe cases of clinical traumatic brain injury and is associated with high mortality and morbidity[1-2]. Diffuse axonal injury is characterized clinically by a rapid progression to coma within 6 hours. The duration of unconsciousness, which has been shown to be strongly related to outcome, depends on the nature and severity of the underlying injury[3-4].

Smith *et al* [5] discovered that injury to the brain stem has a major impact in the pig model of diffuse axonal injury, and that the severity of the injury is positively correlated

with the depth of the coma. In addition, Tokaoka *et al* [6] found that corpus callosum damage in 21 diffuse axonal injury patients correlated with clinical severity, using semiquantitative analysis of magnetic resonance images. Cranial CT is the most important and most common examination for brain injury, because it has high sensitivity for hemorrhage, but not for non-hemorrhagic lesions[4]. With the development of new neuroimaging techniques, such as diffusion-weighted imaging, diffusion tensor imaging, susceptibility weighted imaging and magnetic resonance spectroscopy, the diagnosis rate of diffuse axonal injury has risen[4]. However, the use of these neuroimaging methods for the diagnosis of diffuse axonal injury in patients is controversial because they cannot provide accurate information for clinicians or relatives[7-9].

Many studies have established that somatosensory evoked potential is significantly related to outcome in comatose patients after severe brain injury[10-12]. Carter *et al* [13] found that the prognostic value of somatosensory evoked potential for heavy brain injury was significantly higher than that of the Glasgow coma scale, electroencephalography, computed tomography, papillary responses or motor responses. The disappearance of cortical response N20 is always associated with an unfavorable outcome in patients. Consequently, cortical response N20 is the most reliable prognostic indicator for trauma patients[14-15]. The high usefulness of somatosensory evoked potential for brain injury is not limited to short term outcome (1, 3 months)[16-17]; it is also useful for long term outcome (5 years)[18]. However, somatosensory evoked potential has never been used for determining outcome in prolonged coma diffuse axonal injury patients. We put forth the hypothesis that somatosensory evoked potential can accurately predict outcome in prolonged coma patients with diffuse axonal injury.

## RESULTS

### Quantitative analysis of subjects

A total of 50 diffuse axonal injury patients were admitted in this study. Of these, three patients died and four patients underwent a craniotomy before the somatosensory evoked potential examination. A total of 43 patients (28 males and 15 females) were included in the final analysis.

### Glasgow Outcome Scale score in prolonged coma patients with diffuse axonal injury

The average Glasgow Outcome Scale score of patients with the absence of N20 was 1.80 ± 0.78, which was significantly lower than that of patients in the abnormal (3.05 ± 0.87) and normal (4.14 ± 0.69) groups (Table 1).

### Accuracy of outcome prediction using the somatosensory evoked potential grade in prolonged coma patients with diffuse axonal injury

The outcome of patients with somatosensory evoked potential grade III was always unfavorable. The prognostic accuracy of grade III for unfavorable outcome was 100%, while the prognostic accuracy of grade I for favorable outcome reached 86% (Table 2).

### Accuracy of awakening prediction using the somatosensory evoked potential grade in prolonged coma patients with diffuse axonal injury

The prognostic accuracy of grade III for non-awakening reached 80% while the prognostic accuracy of grade I for awakening was 100%. All patients with somatosensory evoked potential grade I were awake within 6 months of injury (Table 3).

## DISCUSSION

Somatosensory evoked potential is a reliable method for detecting dysfunction of specific nerve conduction pathways. It is not affected by the consciousness of patients or by the anesthetic or sedative at therapeutic doses.

Many studies have established that bilateral absence of cortical somatosensory evoked potential (N20 response) is the most reliable prognostic indicator[14-15, 19]. Christophis[14] discovered that marked changes in N20 represented an unfavorable clinical prognosis in the patient with brain stem injury, and a loss of N20 was closely correlated with a very poor outcome (Glasgow Outcome Scale 1–2), particularly if N20 potential had not recovered within 48 hours. One review of 44 published articles on severe brain injury patients found that about 98.5% of patients with absent N20 had an unfavorable outcome[20]. Robinson *et al* [11] concluded that the absence of N20 in patients with hypoxic-ischemic encephalopathy indicated death or persistent vegetative state. However, several studies reported that the outcome of patients with absent N20 was favorable with Glasgow Outcome Scale ≥ 4. Furthermore, Wohlrab *et al* [21] reported four cases of children with mild or moderate neurological disorder despite having absent N20.

Table 1 Glasgow Outcome Scale (GOS) for prolonged coma patients with diffuse axonal injury and different grades of somatosensory evoked potential (SEP)

| SEP grade | Unfavorable outcome | | | Favorable outcome | |
|---|---|---|---|---|---|
| | GOS 1 | GOS 2 | GOS 3 | GOS 4 | GOS 5 |
| I | 0 | 0 | 1 | 4 | 2 |
| II[a] | 1 | 4 | 9 | 7 | 0 |
| III[ab] | 6 | 6 | 3 | 0 | 0 |

SEPs were graded as normal (grade I) if N20 amplitude and central conduction time (CCT) were normal, abnormal (grade II) if CCT was abnormally prolonged (male > 6.5 ms, female > 6.2 ms) and/or N20 amplitude was < 1.2 μV; absent (grade III) if unilateral or bilateral cortical responses were absent (N20 amplitude was < 0.5 μV) with preserved cervical N13. The higher the GOS, the better the recovery of patients. One-way analysis of variance was used. [a]$P < 0.05$, *vs*. grade I group, [b]$P < 0.05$, *vs*. grade II group.

Table 2 Relationship between somatosensory evoked potential (SEP) grade and accuracy of outcome prediction of prolonged coma patients with diffuse axonal injury

| SEP grade | Predicted outcome (*n*) | | Sensitivity (%) | Specificity (%) | Prognostic accuracy for favorable (%) | Prognostic accuracy for unfavorable (%) |
|---|---|---|---|---|---|---|
| | Favorable (GOS 4–5) | Unfavorable (GOS 1–3) | | | | |
| I | 6 | 1 | 46 | 97 | 86 | 81 |
| II | 7 | 14 | 47 | 46 | 27 | 67 |
| III | 0 | 15 | 50 | 100 | 46 | 100 |

For normal SEP, prognostic accuracy for favorable outcome = (number of patients with SEP grade I and a favorable outcome)/(total number of patients with SEP grade I), prognostic accuracy for unfavorable outcome = (number of patients with SEP grades II and III and an unfavorable outcome)/(total number of patients with SEP grades II and III), sensitivity = (number of patients with SEP grade I and a favorable outcome)/(total number of patients with a favorable outcome), and specificity = (number of patients with SEP grades II and III and an unfavorable outcome)/(total number of patients with an unfavorable outcome).

For abnormal SEP, prognostic accuracy for unfavorable outcome = (number of patients with SEP grade II and an unfavorable outcome)/(total number of patients with SEP grade II), prognostic accuracy for favorable outcome = (number of patients with SEP grades I and III and a favorable outcome)/(total number of patients with SEP grades I and III), sensitivity = (number of patients with SEP grade II and an unfavorable outcome)/(total number of patients with an unfavorable outcome), and specificity = (number of patients with SEP grades I and III and a favorable outcome)/(total number of patients with an favorable outcome). Definitions (calculations) for SEP grade III similar to those for grade II.

GOS: Glasgow Outcome Scale.

Table 3 Relationship between somatosensory evoked potential (SEP) grade and accuracy of awakening prediction of prolonged coma patients with diffuse axonal injury

| SEP grade | Predicted outcome (*n*) | | Sensitivity (%) | Specificity (%) | Prognostic accuracy for awakening (%) | Prognostic accuracy for non-awakening (%) |
|---|---|---|---|---|---|---|
| | Awakening (GOS 3–5) | Non-awakening (GOS 1–2) | | | | |
| I | 7 | 0 | 27 | 100 | 100 | 47 |
| II | 16 | 5 | 29 | 38 | 46 | 24 |
| III | 3 | 12 | 71 | 88 | 82 | 80 |

For normal SEP, prognostic accuracy for awakening = (number of patients with SEP grade I and a favorable outcome)/(total number of patients with SEP grade I), prognostic accuracy for non-awakening = (number of patients with SEP grades II and III and an unfavorable outcome)/(total number of patients with SEP grades II and III), sensitivity = (number of patients with SEP grade I and a favorable outcome)/(total number of patients with a favorable outcome), and specificity = (number of patients with SEP grades II and III and an unfavorable outcome)/(total number of patients with an unfavorable outcome).

For abnormal SEP, prognostic accuracy for non-awakening = (number of patients with SEP grade II and an unfavorable outcome)/(total number of patients with SEP grade II), prognostic accuracy for awakening = (number of patients with SEP grades I and III and a favorable outcome)/(total number of patients with SEP grade I and III), sensitivity = (number of patients with SEP grade II and an unfavorable outcome)/(total number of patients with an unfavorable outcome), and specificity = (number of patients with SEP grades I and III and a favorable outcome)/(total number of patients with an favorable outcome). For SEP grade III, definitions (calculations) were similar to those for grade II.

GOS: Glasgow Outcome Scale.

A bilateral absence of cortical somatosensory evoked potential has been associated with good recovery only in cases of focal lesions disrupting the afferent somatosensory pathway, subdural and subgaleal effusions, following rapid surgical correction of intracranial hypertension and after a lightning strike[18, 22]. Pohlmann-Eden *et al* [17] reported a case of obvious cerebral contusion of the brainstem with a favorable outcome in which N20 recovered on day 9. The patients received somatosensory evoked potential

examination 1 month after injury, which avoided the bleeding and edema peak of diffuse axonal injury. Diffuse axonal injury may severe the axonal projections to the cortex at multiple sites, including the brainstem, which would delay or interrupt central conduction[23-24].

The absence of N20 indicates blockade or destruction of all the neuronal projections from the brainstem to the cortex. Ischemia and anoxia could result in diffuse injury to the cortex and thalamus, which would lead to the absence of N20[19]; the associated outcome in hypoxic-ischemic encephalopathy patients would be persistent vegetative state or brain death[17, 25]. In contrast, in patients with normal somatosensory evoked potential, most regions of the brain continue to receive input (although central conduction time might be prolonged). Consequently, a normal somatosensory evoked potential is a good indicator of favorable outcome and awakening.

In the present study, All diffuse axonal injury patients received somatosensory evoked potential examination 1 month after injury, reducing the possibility of reappearance of N20, and thereby improving the accuracy of the test. Patients with absent N20 in this study had an unfavorable outcome. Thus, absent N20 was a reliable indicator of unfavorable prognosis.

The prognostic value of somatosensory evoked potential for awakening has been examined in numerous studies. Carrai *et al* [26] analyzed 14 clinical studies, and found that 92.2% of normal somatosensory evoked potential exams were associated with awakening, while absent N20 was associated with awakening in only 4.90% of cases. Another review discovered that the awakening rate for bilateral and unilateral loss of N20 was 4% and 52% respectively, while the rate of awakening for patients with normal somatosensory evoked potential was 89%. This review also found that when the somatosensory evoked potential exam was performed 1 month after injury, only 63% of patients with normal somatosensory evoked potential awakened, while both of two patients with absent N20 remained in coma[11]. In the present study, all of seven patients with normal somatosensory evoked potential awoke, which revealed that a normal somatosensory evoked potential could be a reliable indicator for awaking. We observed that 3 out of 15 patients with absent N20 awoke, while 2 out of 3 patients with unilateral absent somatosensory evoked potential awoke.

Cheliout-Heraut *et al* [27] followed five coma patients with unilateral or bilateral absent N20 to the second month, and he discovered that absent N20 reappeared. Therefore, clinicians need to investigate dynamic changes in somatosensory evoked potential over an extended time period in prolonged coma patients.

In summary, the outcome of diffuse axonal injury patients worsened as the somatosensory evoked potential grade rose, and the absence of N20 was a reliable indicator for unfavorable and non-awakening outcome in prolonged coma patients. Furthermore, normal somatosensory evoked potential was closely correlated with awakening.

## SUBJECTS AND METHODS

### Design

A prospective clinical study.

### Time and setting

The study was performed at the First Hospital Affiliated to Medicine College of Zhejiang University, China from January 2010 to January 2012.

### Subjects

Patients were admitted into the First Hospital Affiliated to Medicine College of Zhejiang University for diffuse axonal injury. The diffuse axonal injury characteristics were as follows: (1) The patients had a history of acceleration injury to the head. (2) The clinical manifestations included primary coma after injury, irritability, and no clear signs of nerve dislocation, and without cerebral hypoxia due to asphyxia, hypovolemia or respiratory or cardiac arrest. (3) CT/MRI revealed scattered visible punctate or flaky hemorrhage and edema in the junction of the gray and white matter, corpus callosum, basal ganglia and brain stem (diameter no more than 2 cm), with no obvious shift of the midline (no more than 5 mm). In addition, imaging could be accompanied with subarachnoid hemorrhage without subdural or epidural hematoma or intraventricular hemorrhage. (4) The imaging examination results could be inconsistent with the severe clinical manifestations. The patients met the following selection criteria: (1) traumatic diffuse axonal injury; (2) in coma 1 month after injury; (3) no history of traumatic injury, cerebrovascular accident, intracranial tumor or encephalitis; (4) no complication such as hydrocephalus or intracranial infection 1 month after injury; (5) stable vital signs. After their admission, patients received conservative treatment such as dehydration and hemostasis. The patients who

were in deep coma or suffered neurogenic pulmonary edema received tracheotomy. None of the patients underwent a craniotomy. Family members were informed of the content and objectives of the clinical trial, and we obtained their consent.

## Methods

### *Somatosensory evoked potential recording 1 month after diffuse axonal injury*

Somatosensory evoked potential examinations were performed 1 month after injury with a Keypoint workstation (Dantec Corp., Skovlunde, Denmark). Electrical stimulation of the right and left median nerves was delivered to the wrist by a bipolar surface electrode with stimulus intensity sufficient to cause minimal twitching of the thenar muscles (pulse duration: 0.2 ms; stimulus rate: 5 Hz). Recording stainless steel needle electrodes were placed at Erb's point, spinous process C7, C3' and C4'. Somatosensory evoked potentials were graded as normal (grade I) if N20 amplitude and central conduction time were normal; abnormal (grade II) if central conduction time was abnormally prolonged (male > 6.5 ms, female > 6.2 ms) and/or N20 amplitude < 1.2 μV; absent (grade III) if unilateral or bilateral cortical response was absent (N20 amplitude < 0.5 μV) with preserved cervical N13[26, 28-30] (Figure 1).

### *Glasgow Outcome Scale 6 months after diffuse axonal injury*

The Glasgow Outcome Scale[31] was adopted to assess the outcome 6 months after injury: 1, death; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery. Unfavorable outcome included Glasgow Outcome Scale 1 to 3, while Glasgow Outcome Scale 4 and 5 were defined as favorable outcome. Patients with Glasgow Outcome Scale 3 to 5 were defined as awakening, while Glasgow Outcome Scale 1 and 2 were non-awakening. We calculated and compared the sensitivity, specificity and prognostic accuracy for favorable/unfavorable and awakening/non-awakening outcomes. For normal somatosensory evoked potential, prognostic accuracy for awakening = (number of patients with somatosensory evoked potential grade I and a favorable outcome)/(total number of patients with somatosensory evoked potential grade I), prognostic accuracy for non-awakening = (number of patients with somatosensory evoked potential grades II and III and an unfavorable outcome)/(total number of patients with somatosensory evoked potential grades II and III), sensitivity = (number of patients with somatosensory evoked potential grade I and a favorable outcome)/ (total number of patients with a favorable outcome), and specificity = (number of patients with somatosensory evoked potential grades II and III and an unfavorable outcome)/(total number of patients with an unfavorable outcome).

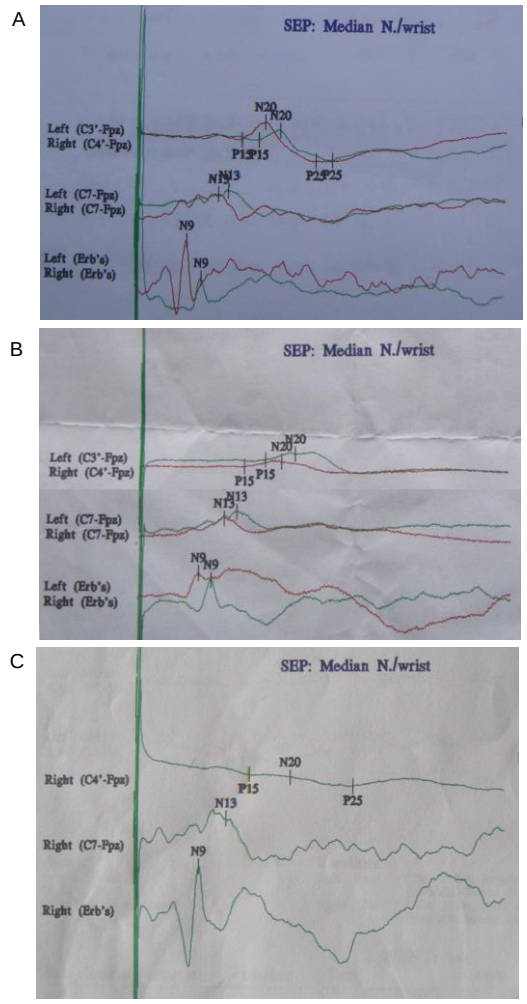


Figure 1 Waveform of different grades of somatosensory evoked potential recording 1 month after diffuse axonal injury.

(A) Normal (grade I): N20 amplitude and central conduction time central conduction time were normal.

(B) Abnormal (grade II): central conduction time was abnormally prolonged (male > 6.5 ms, female > 6.2 ms) and N20 amplitude was < 1.2 μV.

(C) Absent (grade III): Unilateral cortical response was absent (N20 amplitude was < 0.5 μV) with preserved cervical N13.

For abnormal somatosensory evoked potential, prognostic accuracy for non-awakening = (number of patients with somatosensory evoked potential grade II and an unfavorable outcome)/ (total number of patients with somatosensory evoked potential grade II), prognostic accuracy for awakening = (number of patients with somatosensory evoked potential grades I and III and a favorable outcome)/(total number of patients with

somatosensory evoked potential grades I and III), sensitivity = (number of patients with somatosensory evoked potential grade II and an unfavorable outcome)/(total number of patients with an unfavorable outcome), and specificity = (number of patients with somatosensory evoked potential grades I and III and a favorable outcome)/(total number of patients with a favorable outcome). The definitions for somatosensory evoked potential grade III were similar to those for grade II.

### *Statistical analysis*

The data were analyzed utilizing SPSS 16.0 software package (SPSS, Chicago, IL, USA). One-way analysis of variance and Student-Newman-Keuls test were applied. A value of $P < 0.05$ was considered statistically significant.

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**Author contributions:** Xiujue Zheng obtained the funding and served as the director of the test. Mantao Chen participated in analysis of somatosensory evoked potential, the follow-up, and the management of the patients in the hospital. Jingqi Li was responsible for the follow-up and statistical analysis. Fei Cao was in charge of the management of the patients in the hospital, analysis of somatosensory evoked potential, and manuscript writing. All authors approved the final version of the paper.

**Conflicts of interest:** None declared.

**Ethical approval:** The study was approved by the Ethics Committees of First Affiliated Hospital, School of Medicine, Zhejiang University in China.

**Author statements:** The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

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