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Original Article

Risk Factors of Critical Illness Polyneuropathy on Intensive Care Unit Patients

Ji Yeon Hong, M.D., Jong Kyu Kim, M.D., M.S., Ueon Woo Rah, M.D., Ph.D., Seung-Hyun Yoon, M.D., Ph.D., Young-Joo Lee, M.D., Ph.D.[1]

Departments of Physical Medicine and Rehabilitation, [1]Anesthesiology and Pain Medicine, Ajou University School of Medicine, Suwon 443-721, Korea

Objective To find the risk factors of critical illness polyneuropathy (CIP) on intensive care unit patients using early electrodiagnosis.

Method The adult patient who were admitted to the ICU and taken ventilator care with endotracheal intubation were included. The time after admission was 48 to 144 hours. In case of axonal neuropathy of peripheral nerve, if affected nerves were in different two limbs or different three nerves were affected, CIP was diagnosed. If some nerves got abnormal results but did not satisfied the above criteria, the patient was classified as peripheral neuropathy group. The days of using neuromuscular blockade, continuous insulin infusion, catecholamine, vasopressor, corticosteroid, benzodiazepine, parenteral nutrition and fact for continuous renal replacement therapy, SOFA (sequential organ failure assessment) score were evaluated to find the risk factors.

Results Eighteen patients were included. Six patients were CIP and another six were peripheral neuropathy. Risk factors for CIP were age, duration of intensive care, days of neuromuscular blockade and parenteral nutrition ($p < 0.05$). There was no difference on mortality rate among the three groups.

Conclusion The result of early electrodiagnosis on ICU patients for CIP diagnosis revealed that risk factors of CIP were age, duration of intensive care, days of neuromuscular blockade and parenteral nutrition.

Key Words Critical illness polyneuropathy, Risk factor, Electrodiagnosis

INTRODUCTION

Critical illness polyneuropathy (CIP) causes motor weakness of limbs, muscle atrophy, dysesthesia and failure of weaning from mechanical respirator in severe cases even though medical condition that resulted admission is improved.[1] In electrodiagnostic feature, CIP results from axonal injury of peripheral nerves. Main cause of weaning failure might be due to phrenic nerve involvement. Possible causes of CIP are sepsis, systemic inflammatory response syndrome (SIRS) and multiorgan failure. They induce secretion of inflammatory cytokines and excessive immunologic responses. Then endoneural edema and ischemia cause axonal changes of motor and sensory nerves.[2] There are some non-pharmacologic risk factors: multiorgan failure, persistent immobilization, increased blood glucose, septicemia, renal replacement therapy, increased blood urea, low Glasgow coma

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Corresponding author: Jong Kyu Kim
Department of Physical Medicine and Rehabilitation, Ajou University School of Medicine, San 5th, Wonchon-dong, Yeongtong-gu, Suwon 443-721, Korea
Tel: +82-31-219-5281, Fax: +82-31-219-5209, E-mail: jongkyu.kim.md@gmail.com

scale, SIRS, female sex, parenteral nutrition and high score of intensive care unit patients evaluation tools such as APACHE III (acute physiology and chronic health evaluation III) and SOFA (sequential organ failure assessment). Pharmacologic risk factors are aminoglycoside antibiotics, corticosteroids, vasopressors, catecholamines such as epinephrine and norepinephrine and neuromuscular blockades.[2,3]

CIP may delay weaning off from mechanical respirator, but easy recovery has been known.[2] However, it has positive relation to mortality rate. On long term prognosis, some reported persistent pain, sensory change and muscle weakness.[2,4-6] Another study exhibited electrodiagnostic abnormalities after 17 months follow-up.[7] So reducing CIP is very important because it can make some disabilities even if medical treatment is successful.

Purpose of this study is to diagnose CIP with early elecrodiagnostic study on peripheral nerves and to find risk factors for the patients under ventilator care with sepsis in intensive care unit (ICU).

MATERIALS AND METHODS

Subject

Adult patients over-18-year-old under ventilator care after endotracheal intubation in surgical and emergent ICU of Ajou University Hospital were enrolled. Inclusion criteria were 1) patients from third to seventh days (from 48 to 144 hours) of ventilator care days and 2) evidence of sepsis or severe infection (fever, leukocytosis, elevated erythrocyte sedimentation rate and bacterial culture from blood). Exclusion criteria were 1) patients with previous diagnosis as peripheral neuropathy, 2) history of diabetes mellitus more than 5 years ago, 3) immunosuppressed status after organ transplantation, 4) difficulty on electrodiagnosis due to large wound on limbs, 5) ventilator care caused by only brain problem such as cerebral infarction or subarachnoid hemorrhage, 6) taken respiratory support by drug intoxication and 7) no evidence of infection.

Electrodiagnosis

Electrodiagnostic tests were done in the bedside of ICU. Viking Select (VIASYS Healthcare Inc., Wisconsin, USA) were utilized for electrodiagnosis. One upper limb and contralateral lower limb were examined at least. If possible, all four extremities were tested. Motor nerve conduction study was done by tendon-belly method. Sensory nerve conduction was studied antidromically. Reference values were from Liveson and Ma.[8] On compound muscle action potential of median nerve, latency was set 3.9 ms and amplitude was set 5.4 mV as reference values. For sensory nerve action potential of median nerves, latency was set 3.4 ms and amplitude 20 μV for male and 16 μV for female. For ulnar nerve, latency of compound muscle action potential was set 3.3 ms and amplitude 4 mV. On ulnar sensory nerve, latency was set 3.2 ms, amplitude for male patients 15 μV and for female patients 10 μV. Examining lower limbs, latency of deep peroneal motor nerve was set 6.2 ms and amplitude 2.6 mV. Latency of posterior tibial motor nerve was set 6.1 ms and amplitude 5.8 mV. For sensory nerve action potential of superficial peroneal and sural nerves latency was set 4 ms and amplitude 10 μV. All amplitudes were decided by peak to peak value. In upper limbs median and ulnar nerves were examined for motor and sensory nerve conduction study. In lower extremities deep peroneal and posterior tibial nerves were examined for motor nerve conduction study and superficial peroneal and sural nerves for sensory nerve.

CIP-diagnosed group was defined when peripheral nerves of one upper and the other lower limbs both got axonal neuropathy or three or more nerves revealed abnormal axonopathy. When all motor nerves elicited no response for whom took neuromuscular blockade, decision was done only by results of sensory nerves. Patients who did not satisfy above-mentioned diagnostic criteria but some abnormal result of peripheral nerves were categorized as peripheral neuropathy (PN) group.

Risk factors

After electrodiagnosis, medical records were reviewed. Using days of neuromuscular blockade, continuous insulin injection, aminoglycoside antibiotics, catecholamines such as epinephrine and norepinephrine, vasopressors as dopamine and dobutamine, corticosteroids, benzodiazepines as sedative and parenteral nutrition were searched. Continuous renal replacement therapy history was checked also. SOFA was assessed on the very day or nearest day. Six months later, whether the patient discharged alive or died was reviewed by medical record.

Statistics

SPSS 17.0 Statistics (SPSS Inc.) was used for statistical analysis. Kruskal-Wallis test was done for three groups of CIP, PN and normal patients. Spearman's cor-

relation analysis was taken for CIP. Three groups were recategorized into two groups - CIP and non-CIP - and these two groups were taken Mann-Whitney test and Spearman's correlation analysis. In addition, those three groups were recategorized into another two groups - abnormal (CIP and PN) and normal - and Mann-Whitney test and Spearman's correlation analysis were repeated. Six months later, survival was analyzed in the same way for three groups except who was failed follow up.

RESULTS

Demographic feature

Nineteen patients were enrolled. One patient was found history of diabetes mellitus later, so was excluded. Analysis was done for 18 patients. Fifteen were male and three were female. Average age was 61.4 and mean days in ICU were 4.4 days. Six were diagnosed as CIP, another six corresponded PN group and the other six showed normal findings. Eight patients died at ICU, another eight patients survived. Records of two could not be confirmed due to follow up loss (Table 1).

CIP, PN and normal groups

Days on ICU, neuromuscular blockade and parenteral nutrition showed significant difference among three groups ($p<0.05$). Because there is no patient using aminoglycoside antibiotics, this item was excluded in analysis. Result from correlation analysis, age, days on ICU, neuromuscular blockade and parenteral nutrition exhibited significant positive correlations (Table 2). There was no

Table 1. Characteristics of Enrolled Patients

No	Sex	Age	Days	Sepsis etiology	Result of electrodiagnosis	Survival
1	M	78	7	Post-surgical	Critical illness polyneuropathy	Dead
2	M	65	7	Medical	Peripheral neuropathy	Dead
3	M	62	3	Post-surgical	Peripheral neuropathy	NR
4	M	52	3	Post-surgical	Peripheral neuropathy	Survive
5	M	40	4	Medical	Peripheral neuropathy	Survive
6	M	77	5	Medical	Critical illness polyneuropathy	Dead
7	M	77	3	Post-surgical	Peripheral neuropathy	Dead
8	M	67	3	Post-surgical	Peripheral neuropathy	Dead
9	F	69	5	Post-surgical	Critical illness polyneuropathy	Survive
10	M	55	3	Post-surgical	Normal electrodiagnosis	Survive
11	M	73	3	Medical	Normal electrodiagnosis	Dead
12	M	52	6	Post-surgical	Critical illness polyneuropathy	Dead
13	M	79	6	Post-surgical	Critical illness polyneuropathy	Dead
14	F	72	6	Post-surgical	Critical illness polyneuropathy	Survive
15	M	74	4	Medical	Normal electrodiagnosis	NR
16	M	25	4	Post-surgical	Normal electrodiagnosis	Survive
17	F	47	5	Post-traumatic	Normal electrodiagnosis	Survive
18	M	41	3	Post-surgical	Normal electrodiagnosis	Survive

Days: Days on intensive care unit. NR: No record about survival

Table 2. Result of Kruskal-Wallis Test and Spearman's ρ Correlation Analysis among Critical Illness Polyneuropathy, Peripheral Neuropathy and Normal Group

	Age	Days	SOFA	NMB	Insulin	Catech	Dopa	Steroid	Bzp	CRRT	PN
χ^2	4.442	8.22	3.87	9.658	2.474	1.889	2.037	0.316	5.657	1.063	6.139
Sig.	0.108	0.01	0.146	0.004	0.324	0.399	0.452	1	0.064	1	0.039
P	0.486	0.606	0.258	0.484	0.36	0.33	0.3	0.092	0.042	0	0.597
Sig.	0.041	0.008	0.301	0.042	0.142	0.181	0.227	0.718	0.87	1	0.009

Days: Days on intensive care unit. SOFA: Sequential organ failure assessment. NMB: Neuromuscular blockade. Catech: Catecholamine. Dopa: Dopamine. Bzp: Benzodiazepine. CRRT: Continuous renal replacement therapy. PN: Parenteral nutrition

Table 3. Result of Mann-Whitney Test and Spearman's ρ Correlation Analysis between Critical Illness Polyneuropathy and non-Polyneuropathy Group

	Age	Days	SOFA	NMB	Insulin	Catech	Dopa	Steroid	Bzp	CRRT	PN
χ^2	4.254	8.219	0.009	8.519	1.06	1.166	2.037	0.014	1.781	0.266	5.17
Sig.	0.108	0.01	0.146	0.004	0.324	0.399	0.452	1	0.064	1	0.039
P	0.486	0.606	0.258	0.484	0.36	0.33	0.3	0.092	0.042	0	0.597
Sig.	0.041	0.008	0.301	0.042	0.142	0.181	0.227	0.718	0.87	1	0.009

Days: Days on intensive care unit. SOFA: Sequential organ failure assessment. NMB: Neuromuscular blockade. Catech: Catecholamine. Dopa: Dopamine. Bzp: Benzodiazepine. CRRT: Continuous renal replacement therapy. PN: Parenteral nutrition

Table 4. Result of Mann-Whitney Test and Spearman's ρ Correlation Analysis between Peripheral Neuropathy and Normal Group

	Age	Days	SOFA	NMB	Insulin	Catech	Dopa	Steroid	Bzp	CRRT	PN
χ^2	1.978	2.125	3.059	0.286	2.386	1.629	0.509	0.287	1.077	0.266	3.958
Sig.	0.160	0.145	0.08	0.593	0.122	0.202	0.476	0.592	0.299	0.606	0.047
P	0.341	0.354	0.424	0.13	0.375	0.31	0.173	0.13	−0.252	−0.125	0.483
Sig.	0.166	0.15	0.079	0.608	0.126	0.211	0.492	0.607	0.314	0.621	0.043

Days: Days on intensive care unit. SOFA: Sequential organ failure assessment. NMB: Neuromuscular blockade. Catech: Catecholamine. Dopa: Dopamine. Bzp: Benzodiazepine. CRRT: Continuous renal replacement therapy. PN: Parenteral nutrition

significant difference on survival rate. There also was no difference for CIP, PN and normal categories between survival and mortality groups.

CIP versus non-CIP groups

There was significant difference on age, days on ICU, neuromuscular blockade and parenteral nutrition between CIP and non-CIP groups. Correlation analysis exhibited positive correlations on age, days on ICU, neuromuscular blockade and parenteral nutrition (Table 3). On survival rate, there was no difference. Also there was no distinction between survival and mortality groups for CIP and non-CIP categories.

Normal versus abnormal groups

Analyzing normal versus abnormal groups showed significant difference only in parenteral nutrition item. Correlation analysis also exhibited significant positive correlation in parenteral nutrition item (Table 4). No difference on mortality rate was found from two groups. Mortality versus survival groups analysis for normal and abnormal groups did not show any difference.

SOFA score and mortality rate

No significant difference between mortality and SOFA score was found. In correlation analysis, some negative correlation appeared, but it did not have significance (ρ =−0.465, p=0.07).

DISCUSSION

This study is the first research to find risk factors of CIP using early electrodiagnosis. Some studies investigated risk factors retrospectively only for patients who had been diagnosed CIP. Other studies screened just very severe sepsis patients and proceeded the research.[9] This study screened ventilator cared patients for respiratory failure and identified severity of sepsis using SOFA score and correlations with CIP development.

Multiorgan failure associated sepsis can be predicted by SOFA. The initial, the worst and the average score is related with mortality rate.[10,11] APACHE III score is usually utilized for ICU patients. Highest APACHE III score during first 24 hours reflects mortality rate very well. But it requires 17 kinds of physiological laboratory results and they have to be summated with age and chronic health status. So its utility has some difficulty because it is very complicated.[12,13] By contrast, SOFA consists of six items, and each item has score

ranging from 0 to 4, so total score ranges from 0 to 24. It is easy to use and needs fewer tests. According to the study of de Letter et al.[14] high APACHE III score and SIRS were risk factors for CIP development and Bednarik et al.[15] reported patients with CIP showed significant higher SOFA score.

Leijten et al.[4] reported that CIP patients showed higher mortality rate than others for ventilator cared people more than seven days and Garnacho-Montero et al.[5] exhibited that mortality of CIP patients had seven times more in-hospital mortality than other for sepsis patients treated with mechanical respirator more than 9 days. In our study, there was no difference for mortality rate and SOFA score for disease severity. Cause of increased mortality in CIP patients may be due to prolongation of ventilator care time and increasing medical complications. Our study did not check total days of ventilator care hence we could not identify time extension of ventilator care. Our study did not revealed any difference on SOFA score and mortality rate. We had small sample size and some cases were missed, so it is hard to conclude that CIP had no influence to mortality rate.

Our study just utilized classical nerve conduction tests for peripheral nerves in diagnosing CIP. There were some researches using needle electromyography to limb muscles or phrenic nerve conduction test, but we decided not to examine intensively cared patients with various invasive techniques. Also several kinds of medical equipment interfered us to keep the accuracy of the electrodiagnosis.[1,7,16] Instead, we applied strict diagnostic criteria for CIP, furthermore we made a new category of peripheral neuropathy when some abnormalities were shown but did not satisfy the criteria. Then correlation analyses were done for each three groups. For patients treated with neuromuscular blockade, previous studies excluded these cases or tested with repetitive stimulation then exclude the patients who exhibited decreased amplitude of compound muscle action potential. Neuromuscular blockade such as vercuronium is well-known risk factor for CIP, hence we did not exclude those patients. In these cases, we decided to diagnose from sensory nerve action potentials only.[9,15,17] Critical illness myopathy (CIM) reveals similar clinical and electrodiagnostic manifestations. CIM causes muscle weakness due to muscle fiber necrosis.[2] Because CIM does not involve sensory nerves originally, result of sensory nerve conduction study exhibits normal findings usually.[18] For distinguishing CIM from CIP, needle electromyography and direct muscle stimulation test are necessary, but we did not.[16] In our study, all of six patients who were diagnosed as CIP exhibited abnormalities of sensory nerve action potentials. Therefore there was rare possibility to influence the result from misdiagnosis.

Khan et al.[9] reported that 45% of severe sepsis patients exhibited abnormal nerve conduction study at 3 days and compatible findings with CIP in 50% at 21 days. Each week follow up study exhibited progressive decrease in amplitude of compound muscle action potential. These results support benefit of early screening for CIP. Subjects who revealed abnormal result but did not satisfy diagnostic criteria of CIP may be similar with PN group of our study. Focal peripheral neuropathy, not polyneuropathy, can be evolved by some causes including focal nerve compression in ICU treatment. Another possibility for PN group is early manifestation of vulnerable nerve axons in disease progression of CIP. So even if early electrodiagnosis reveals only a few abnormal findings not satisfying CIP diagnosis criteria and if the abnormal findings include axonal neuropathy, possibility of CIP has to be kept in mind.

Our study reveals four risk factors, age, days on ICU, neuromuscular blockade and parenteral nutrition. Analysis of diseased group versus normal group exhibits a positive correlation only in parenteral nutrition. This supports that diseased nerves in PN group is not due to CIP but due to other etiology. The fact that other statistic result comparing CIP and other group exhibits higher correlation coefficient than the original analysis supports above mentioned conclusion. It is not well known whether CIP develops in all four limbs simultaneously or abnormality of some vulnerable nerves progress to mononeuropathy multiplex and finally CIP. Some reports using early screening defined CIP even when focal abnormal findings of peripheral nerve existed. But our study exhibited that CIP might be involved in multiple nerves simultaneously. Therefore diagnosis of CIP using electrodiagnosis requires attention. Risk factors from our study were well known items from other study. Renal replacement therapy, insulin and vasopressor did not show significant result. That might be due to small numbers of corresponding patients.[2] Our study could not reveal any correlation between SOFA and CIP development. This was because neuromuscular blockade took more roles than sepsis severity in CIP development. However there was possibility of errors in calculating SOFA score because the calculation was done retro-

spectively by medical records and timings of SOFA score and electrodiagnosis were not identical.

Main complication of CIP is ventilator weaning failure. However, many studies reported neuromuscular sequelae after discharge in survived patients.[2,7] There was a report that poor clinical outcome of CIP correlates with severe electrodiagnostic findings.[1] CIP causes paresthesia and muscle weakness due to axonal change, so these complications may take longer than demyelination neuropathy for recovery. Many had attempted treatment for CIP. A small sized study reported protective effect of immunoglobulin. Other studies had tried using steroids for prevention, but there had been no significant result. Rather, physical therapy and rehabilitation is effective for prevention of joint contracture and pressure sore.[19,20] Thus reducing risk factors and immediate rehabilitation with early diagnosis is very important in CIP.

Limitations of our study were that we had small sample size and timing of examination ranges somewhat widely from third to seventh days. Another limitation was that severe sepsis patients and less severe patients were enrolled in the same category. Defining severe sepsis patients clearly is very difficult. Our study checked SOFA score and took correlation analysis for correction of disease severity. Many kinds of equipment in ICU had interfered electrodiagnostic test practically. We did not utilize needle electromyography. Confirmative pathologic tests such as nerve or muscle biopsy were not done either. Another limitation was not having follow up electrodiagnosis. Risk factors about disease prognosis and recovery were not investigated. For elucidating affecting factors of CIP development, prognosis and recovery more and larger sized prospective study including long term follow up may be necessary.

CONCLUSION

Six patients (33.3%) were diagnosed as CIP among 18 patients who took electrodiagnostic test from third to seventh day under ventilator care after endotracheal intubation in ICU. On the investigation of risk factors, there were significant correlations on CIP with older age, more days in ICU, neuromuscular blockade and parenteral nutrition. In the future, large prospective study would be necessary under more strict condition.

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