2014년 8월 박사학위 논문

2014년 8월

박사학위 논문

외상 후 감각이상 환자에 대한 외상성 말초 삼차신경 병변 진단기준 적용 및 지속적 신경병변의 위험인자 분석

진단기준 적용 및 지속적 신경병변의 위험인자 분석
외상 후 감각이상 환자에 대한 외상성 말초 삼차신경 병변

조선대학교 대학원

치 의 학 과

유 지 원

유 지 원

외상 후 감각이상 환자에 대한 외상성 말초 삼차신경 병변 진단기준 적용 및 지속적 신경병변의 위험인자 분석

Application of peripheral traumatic trigeminal neuropathy criteria to patients with altered sensation after trauma and outcome predictors affecting permanent neuropathy

2014년 8월 25일

조선대학교 대학원

치 의 학 과

유 지 원

외상 후 감각이상 환자에 대한 외상성 말초 삼차신경 병변 진단기준 적용 및 지속적 신경병변의 위험인자 분석

지도교수 윤 창 륙

이 논문을 치의학 박사학위신청 논문으로 제출함.

2014년 4월

조선대학교 대학원

치 의 학 과

유 지 원

유지원의 박사학위 논문을 인준함

위원장　조선대학교　교수　김 홍 중　(인)

위　원　조선대학교　교수　윤 창 륙　(인)

위　원　조선대학교　교수　국 중 기　(인)

위　원　연세대학교　교수　최 종 훈　(인)

위　원　연세대학교　교수　김 성 택　(인)

2014년　6월

조선대학교 대학원

목 차

표 목 차

초록

외상 후 감각이상 환자에 대한 외상성 말초 삼차신경 병변 진단기준 적용 및 지속적 신경병변의 위험인자 분석

유 지 원
지도교수 : 윤 창 륙
조선대학교 대학원 치의학과

연구목적: 본 연구는 외상 후 감각이상 및 통증을 호소하는 환자에게 외상성 말초 삼차신경 병변의 진단기준을 적용하였을 경우 그 유용성을 평가하고, 환자의 주관적, 객관적 특성을 비교 분석하여 지속적인 신경손상의 가능성에 대한 위험인자를 분석하고자 함이다.

연구대상 및 연구 방법: 본 연구는 삼차 신경 영역의 외상 후 감각이상 및 통증을 호소하는 환자를 대상으로 후향적 연구를 시행하였다. 환자의 증상 지속 기간에 따라 3개월 이내 증상이 경감된 환자는 일시적 신경손상, 3개월 이상 증상이 지속된 경우는 지속적 신경손상 군으로 분류하였다. 지속적인 신경손상 병변의 위험인자를 평가하기 위하여, 진료기록을 토대로, 환자 병력에 따른 증상의 평가, 방사선사진 상 신경손상의 징후, 임상적 이학검사, 전류인지 역치 검사 결과를 비교하여, 각 그룹 간 유의성 있는 변수에 대해 다중회귀분석을 시행하였다. 또한, 외상성 말초 삼차신경 병변 기준을 적용하여, 민감도, 특이도, 양성 예측도, 음성예측도를 평가하였다. 다중회귀분석 상 유의성 있는 변수를 토대로, 지속적 신경손상을 평가하는 기준을 재정립하여, 해당 기준의 민감도, 특이도, 양성 예측도, 음성예측도를 산출하였다.

결과: 연구기간 내, 총 111명의 환자가 삼차신경 영역 외상 후, 감각 이상 및

통증을 호소하였으며, 일시적 신경손상 군은 23명, 지속적 신경손상 군은 88명이었다. 외상성 말초 삼차신경 병변 기준의 민감도, 특이도를 산출한 결과, 낮은 민감도, 높은 특이도를 나타내었다. 지속적 신경손상 군은 일시적 신경손상 군에 비해 파노라마 방사선 상 신경 손상의 징후, 이학 검사 상, 핀 자극 시 감각저하 및 자극이 방사상으로 퍼지는 증상, 접촉 자극 시 자극이 방사상으로 퍼지는 증상, 이질통이 통계학적으로 유의성 있게 나오는 결과를 보였다. 이를 토대로 다중 회귀분석을 시행한 결과, 파노라마 방사선 사진 상 신경 손상의 징후, 핀 자극시 감각저하, 핀 자극 및 접촉 자극 시 방사상으로 퍼지는 증상이 집단에 영향을 끼치는 것으로 나타났으며, 설명력은 60.7%로 나타났다.

결론: 본 연구 결과, 삼차신경 영역의 외상 후 감각이상 또는 통증을 호소하는 환자에게 외상성 말초 삼차신경 병변 기준의 적용은 실질적으로 유용하다 볼 수 있다. 그러나 외상 직후 증상의 지속 여부를 예측하는 위험인자의 보완은 특히 의원성 외상의 경우, 감각이상의 발생한 환자의 예후 평가 및 환자의 기대수준을 적절하게 설정하는데 도움이 될 수 있다. 추후 많은 환자군을 대상으로 다기관 평가를 시행할 경우, 본 연구를 보완하여, 보다 정확한 위험인자 예측을 하는 것이 필요할 것이다.

주제어: 삼차신경, 신경손상, 위험인자, 외상, 의원성, 민감도, 특이도

Ⅰ. Introduction

Nerve damage from variety of factors can cause chronic neuropathic pain. Iatrogenic nerve damage, especially, can result in medico-legal issues. In dentistry, the treatment itself is the surgical approach, and can cause harm to the peripheral nerve, which in the orofacial area is a portion of the trigeminal nerve. Dental treatments with reports of nerve injury include the Caldwell-Luc intervention, orthognathic mandibular advancement surgery, extrusion of root canal filling material, administration of local anesthetic, and implant surgery, with third molar extraction as the most frequent cause.[1,2] All these changes can be transient or persistent depending on the degree of the the nerve insult.[3]

Nerve damage can affect a single nerve or several nerves, and result in sensory, motor, and/or autonomic deficits in the affected region.[2] Damage to sensory nerves can result in anesthesia, paraesthesia, pain, or a combination of the three. The resulting pain could also create significant functional problems.[4] Patients with trigeminal nerve trauma often complain that the sensory disturbance and/or pain interfere with daily function, decreasing quality of life and potentially leading to significant psychosocial problems.[5] The significant disability associated with these nerve injuries may also result in increasing numbers of medico-legal claims.[4]

According to the report of the Korea Consumer Agency, out of 302 cases seeking legal redress for dental treatment, 101 cases (33.4%) were compensated and reimbursed. The number of cases of sensory alteration was 34, 11.3% of all medico-legal claims. The average amount of indemnity was 9,670,000 (KRW) in cases of lingual nerve

injury (LNI), and 6,230,000 (KRW) in those of inferior alveolar nerve injury (IANI). Especially, in cases of dental implant placement, the indemnity was judged about 31,360,000(KRW).

Because of these high indemnities, and for the patients' and clinicians' own well-being, clinicians should make particularly strong efforts to prevent iatrogenic nerve damage. However, if patients complain about altered sensation and/or pain after dental procedures, these patients should be reassessed for their conditions, medically managed for them when needed, and referred to orofacial pain or oromaxillofacial surgical specialists for proper treatment. In addition, orofacial pain or oromaxillofacial surgical specialists should diagnose their conditions properly, and assess risk factors for chronic neuropathy, to provide them with realistic outcome expectations.

Unfortunately, neuropathic pain due to trigeminal injury has been poorly defined. There are no standards or physical examinations to diagnose these conditions. In a recent article, diagnostic criteria for "Peripheral Painful Traumatic Trigeminal Neuropathy (PPTTN)" were proposed.[6] The authors tried to characterize the condition and coordinate it with the International Headache Society (IHS) criteria. In that study, clinical phenotypes were compared between PPTTN patients and classical trigeminal neuralgia, and the study concluded that PPTTN criteria could be clinically useful. However, the clinical symptoms and pathophysiology of these two disorders are completely different. In addition, applying these criteria in clinics would require evaluation of the PPTTN criteria for both sensitivity and specificity. The main target population would be patients with altered sensation and/or pain, which is the typical symptom of PPTTN.

To our knowledge, there have been no studies evaluating the sensitivity and specificity of PPTTN criteria, and assessing the risk factors of permanent nerve damage.

Consequently, the aims of this study were to evaluate the validity and reliability of PPTTN criteria for patients with altered sensation and/or pain by evaluating their sensitivity and specificity, and to determine outcome predictors affecting permanent neuropathy.

Ⅱ. Materials and Methods

A. Subjects

This was a retrospective study of patients who complained of altered sensation or pain following trigeminal nerve trauma, from 2010 to 2013, who were visiting the Department of Oral Medicine, Chosun University, Dental Hospital.

This study was not confined to patients with iatrogenic nerve damage. Trigeminal neuropathic symptoms after fractures or traffic accidents could also be subjects of insurance claims, so these cases were also included.

Patients with trigeminal neuropathy caused by systemic disease or local inflammation were excluded in this study. In addition, studied population was confined to the distribution of the trigeminal nerve third branch, i.e., symptoms affected to the first and second branches of the trigeminal nerve were excluded.

This study was approved by the institutional review board of Chosun University, Dental Hospital, 2013.

B. Methods

The patient histories and clinical examinations were documented according to routine procedures for sensory alteration after trauma in the Department of Oral Medicine, Chosun University, Dental Hospital. Demographic data collected from each patient included age of onset and gender. From consecutive records, patients for whom the symptoms resolved in less than 3 months were designated the “transient group”. The “persistent group” was comprised of patients whose symptoms continued for more than 3 months after trauma, according to patient history or

consecutive records. From the included population's medical records, variables were collected for comparison with those of the previous study.[6)]

1. Variables from patient history

Pain intensity was measured using a visual analogue scale (VAS), where 0 was no pain and 10 was worst pain imaginable. To match variables with the previous study,[6)] the quality of the pain was adjusted by one doctor (Ryu JW) after reviewing the medical records, who chose one or more of the following descriptive terms: electrical, stabbing, throbbing, pressure, burning, or any combination of the five terms. This was the same for the temporal patterns, adjusted according to attack frequency and duration parameters: episodic, daily, and continuous. Patients were asked to report the pain duration representing that of a typical attack. The presence of autonomic signs such as tearing, redness, or swelling was also recorded. Patients were asked about their quality of sleep after the symptoms started. A trauma history was collected verbally and from relevant documentation (e.g., third molar extraction, dental implant, traffic accident, fracture of jaws, etc.).

2. Variables from clinical examination

The clinical examination included mechanosensory testing, and radiographic examination, to assess the subjective symptoms of patients. Mechanosensory testing of the affected and contralateral areas included the use of pinprick stimuli (with a dental explorer) and blunt stimuli (with cotton swabs). Except for patients with lingual nerve damage only (6 cases), all mechanosensory tests were given to the extraoral affected area. During the test, patients were asked to rate of response to each stimulus based on a scale of 0 to 100, such that 0 meant a complete sensory

deficit to the given stimulus, while 100 meant the same intensity of feeling as that of the contralateral area. When patients reported sensitivity over 100 (hypersensitivity), they were asked to rate the feeling numerically (>100). These tests were complemented by examining the radiating sensation caused by each stimulus. For statistical analysis, the scores of each stimulus were categorized into 4 degrees: very low (0-39), low (40-79), normal (80-119) and high (120-). The mechanosensory tests were repeated three times. Based on these tests, affected areas were diagnosed as to "sensory signature" to match the diagnoses of the previous study.[6] In addition, patients who agreed to further evaluation procedures for defining their symptoms underwent quantitative sensory testing (QST) using transcutaneous electrical stimuli delivered by the Neurometer Nervscan NS3000 device (Neurotron). The Neurometer QST procedures were matched with another previous study that evaluated neurosensory alteration in orthognathicsurgeries.[7] Stimuli were delivered at 250 Hz to assess the sensory threshold associated with A-δ fiber stimulation, and at 2,000 Hz and 5 Hz for A-β and C fiber evoked sensory thresholds, respectively. Subjects were instructed to release a control button upon the first sensation. Both operator and patients were blinded to the stimulus intensity provided. The scores obtained with each stimulus were converted ratios, of the affected area to the contralateral area.[6]

All patients underwent panoramic radiographic examination to evaluate the nerve injury. Additional cone beam computed tomography (CBCT) imaging was taken to patients who agreed to further evaluation in order to locate and grossly assess the extent of nerve damage.

3. Application to PPTTN criteria

From medical records, symptoms related to trigeminal neuropathy were

evaluated according to PPTTN criteria. Sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated on each items, and final diagnoses. Item B (duration) was excluded, because the duration of the symptoms was the criterion by which the studied population was grouped.

4. Determination of outcome predictors affecting permanent neuropathy

To find out the statistical differences between the transient and persistent groups, statistical analysis was performed via Pearson's chi-square test (χ^2). Differences between continuous variables (onset age and pain intensity) were analyzed with Student's *t*-test.

To explore possible contributing factors affecting the permanence of nerve injury, the above variables with significant differences were analyzed with multiple regression analysis.

Based on the results of the regression analysis, the variables with significance were placed on the items according to their respective PPTTN criteria. Sensitivity and specificity, PPV, and NPV were calculated for each item, and for diagnoses of outcome predictors.

C. Statistical Analyses

Data were analyzed with SPSS version 18 for Windows (SPSS, Chicago, Illinois, version 18.0).

Statistical significance was defined as $p < 0.05$, with a 95% confidence interval.

Ⅲ. Results

In total, 111 patients were collected for the study, of whom 5.4% presented with LNI (6 patients) and 94.6% with IANI (96 patients). The transient group was comprised of 23 patients and the persistent group was comprised of 88 patients.

A. Comparison of patient profiles between the transient and persistent groups

The demographic features of each group are summarized in Table 1. There were no differences in onset age or gender ratio between groups.

In evaluation of the location, the left side was affected in 50 cases (45.05%), and the right side was in 48 cases (43.24%). Both sides (mentum area) were affected in 13 cases (11.71%).

Table 1. Demographic findings in studied population

Group	Onset age (y±SD)	Gender(M;F ratio)
Transient(n=23)	40.30±16.25	8:15
Persistent(n=88)	46.51±15.27	35:53
Total(n=111)	45.23±15.61	43:68

M:F ratio, male:female ratio.
Onset age was presented as mean year±standard deviation.

The distributions of initiating events causing altered sensation or pain are summarized in Table 2, while the differences between patient profiles in the transient and persistent groups are described in Table 3. Patients in the transient group mostly reported the quality of pain to be pressure (73.90%), while the persistent group mostly reported burning pain (60.20%). Within groups, there were no significant differences in quality descriptors (χ^2, $p > 0.05$).

Table 2. Distributions of initiating events affecting altered sensation or pain

Causes	Cases	Percentages(%)
Anesthesia	3	2.70
Mass excision	5	4.50
Endodontic treatment	9	8.11
Third molar extraction	25	22.52
Fracture of mandible	18	16.22
Orthognathic surgery	8	7.21
Incision and drainage	1	0.90
Implant placement	31	27.93
Operative/Periodontic treatment	5	4.50
Wound	6	5.41

Pain intensity showed no differences in VAS scores between groups. The average (± SD) scores of pain intensity were 5.09± 1.98, and 5.48± 1.97 in the transient and persistent groups, respectively.

In evaluation of temporal patterns, most patients reported continuous (87% and 90.90% in the transient and persistent groups, respectively) pain, with no significant differences between groups.

For 35 patients, quality of sleep was reported as bad because of the trauma. This variable was not statistically different between the groups.

In the radiographic imaging tests, there was a significant difference ($p < 0.05$) in the panoramic view test. All patients underwent panoramic radiographs, and 59 patients (53.15%) also underwent CBCT imaging of the area. There were 14 positive signs of nerve damage using CBCT out of 46 cases (30.43%), while in panoramic view there were no sign.

Table 3. Differences between patient profiles in transient and persistent group

Parameter		Transient(n=23)	Persistent(n=88)	Statistics
Intensity (mean VAS±SD)		5.09±1.98	5.48±1.97	T, p=0.399
Temporal pattern		Daily=3(13.00%) Continuous=20 (87%)	Daily=8(9.10%) Continuous=80 (90.90%)	χ^2, p=0.695
Autonomic signs		No=22(95.70%) Yes=1(4.30%)	No=85(96.60%) Yes=3(3.40%)	χ^2, p=1.000
Sleep quality		No change= 16(72.70%) Bad=6(27.30%)	No change= 55(65.50%) Bad=29(34.50%)	χ^2, p=0.439
Quality of Pain	Electric	No=15(65.2%) Yes=8(34.80%)	No=47(53.40%) Yes=41(46.60%)	χ^2, p=0.310
	Stabbing	No=15(65.2%) Yes=8(34.80%)	No=58(65.90%) Yes=30(34.10%)	χ^2, p=0.950
	Throbbing	No=23(100%) Yes=0(0%)	No=84(95.50%) Yes=4(4.50%)	χ^2, p=0.579
	Pressure	No=6(26.10%) Yes=17(73.90%)	No=36(40.90%) Yes=52(59.10%)	χ^2, p=0.192
	Burning	No=12(52.20%) Yes=11(47.8%)	No=35(39.80%) Yes=53(60.20%)	χ^2, p=0.284
Panoramic view result		Yes=9(30.40%) No=14(60.90%)	Yes=56(63.60%) No=32(36.40%)	χ^2, p=0.034*

SD, standard deviation of mean value; T, Student's *t*-test; χ^2, Pearson's chi-square test.

* $p<0.05$ (by Pearson's chi-square test).

In the results of mechanosensory testing, most patients suffered from reduced sensation compared to the contralateral area (Table 4). With blunt mechanical stimulus from cotton swabs, 73.90% of the transient and 60.90% of the persistent group reported reduced sensation. With pin stimulus, 69.50% of the transient and 58.60% of the persistent group

reported reduced sensation. Between groups, there was a statistically significant difference in the result of the pinprick test ($p < 0.05$). Radiating symptoms after blunt and pinprick stimuli were also significantly different between groups.

Eleven patients in the transient and 67 patients in the persistent group underwent the QST procedures with the Neurometer. The ratios of the scores (affected area : contralateral area) in A-β, A-δ, and C fibers were all significantly higher than expected, but between the groups, there were no differences.

Table 4. Differences between results of mechanosensory testing in transient and persistent group

Parameter		Transient(n=23)	Persistent(n=88)	p-value
Physical exam	Blunt stimulus	Very low=11(47.80%) Low=6(26.10%) Normal=2(8.70%) High=4(17.40%)	Very low=18(20.70%) Low=35(40.20%) Normal=10(11.50%) High=24(27.60%)	p=0.074
	Radiating after blunt stimulus	No=17(73.9%) Yes=6(26.10%)	No=29(33%) Yes=59(67%)	p=0.000***
	Pin stimulus	Very low=13(56.50%) Low=3(13.00%) Normal=0(0.00%) High=7(30.40%)	Very low=23(26.40%) Low=28(32.20%) Normal=13(14.90)%) High=23(26.40%)	p=0.012*
	Radiating after pin stimulus	No=19(82.60%) Yes=4(17.40%)	No=38(43.20%) Yes=50(56.80%)	p=0.0001**

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ (by Pearson's chi-square test).

Diagnoses of sensory signatures are described in Table 5. In the transient group, hypoesthesia and hypoalgesia were the main features of the sensory signature. In the persistent group, hypoesthesia, hypoalgesia, and allodynia were the main features. Between groups, there was a statistically significant difference in the allodynia signature ($p < 0.01$).

Table 5. Diagnoses of sensory signatures

Sensory signatures		Transient	Persistent	p-value
Hypoalgesia	No	7(30.40)	30(34.10)	0.741
	Yes	16(69.60)	58(65.90)	
Hyperalgesia	No	16(69.60)	64(72.70)	0.763
	Yes	7(30.40)	24(27.30)	
Hypoesthesia	No	4(17.40)	24(27.30)	0.331
	Yes	19(82.60)	64(72.70)	
Hyperesthesia	No	19(82.60)	64(72.70)	0.331
	Yes	4(17.40)	24(27.30)	
Allodynia	No	16(69.60)	27(30.70)	0.001**
	Yes	7(30.40)	61(69.30)	

** $p<0.01$ (by Pearson's chi-square test).

B. Outcome predictors affecting persistent neuropathic symptoms

Based on the chi-square and *t*-tests, the variables with significant differences between groups were identified: panoramic view result, reduced sensation, and radiation in the pinprick test, radiation in the blunt stimulus test, and allodynia. Multiple regression analysis was then performed on these variables (Table 6). The results revealed that the presence of a neurologic lesion in the panoramic view result, reduced sensation in the

pinprick test, and radiation in the pinprick test could affect the persistent group, with Nagelkerke's R^2 calculated to be 0.607.

Table 6. Outcome predictors affecting persistent neuropathy

Parameters	β	Wald	Nagelkerke R^2	Exp(B)
Panoramic view result	1.449	7.751**	0.607	4.258
Normal or exaggerated sensation in the pinprick test	-0.536	1.405		0.585
Reduced sensation in the pinprick test	-2.018	5.778*		0.133
Radiating after blunt stimulus	1.749	1.273		5.751
Radiating after pin stimulus	1.917	5.606*		6.798
Allodynia	-0.232	0.022		0.793

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ (by the Wald test).

C. Sensitivity, specificity, PPV, and NPV for PPTTN criteria

Table 7 showed estimates for sensitivity, specificity, PPV, and NPV for the individual items of the PPTTN criteria (A, C to E) and final diagnosis. Each item showed sensitivities ranging from a low of 20.72% for "not attributed to another disorder" to a high of 36.36% for "imaging or neurophysiologic sign". Sensitivity of item C (clinical evident sign) was not calculated because all patients showed at least one clinically evident neurologic dysfunction. Specificities ranged from 79.28% for "at least one clinical evident neurologic dysfunction" to 83.15% for "imaging or

neurophysiology demonstrating a neurologic lesion and its location". Possible, probable, and definite PPTTN criteria were observed to have sensitivities of 13.04, 13.04, and 39.13 % and specificities of 94.32, 94.32, and 79.55 %, respectively. The PPVs for the PPTTN criteria A, and C to E are 9.09 to 100%, and the NPVs are 0 to 94.32%.

In this study, application to criteria of PPTTN provided low sensitivity and PPV, although specificity and NPV were relatively high.

Table 7. Sensitivity, specificity, PPV, NPV of individual criteria, and final diagnoses of PPTTN criteria

Diagnostic criteria and Diagnostic level	Sensitivity	Specificity	PPV	NPV
A. spontaneous or touch-evoked pain predominantly affecting the receptive field of one or more divisions of the trigeminal nerve	28.57	80.58	9.09	94.32
C. at least one clinically evident neurologic dysfunction	-	79.28	0.00	100.00
D. imaging or neurophysiologic demonstrating a neurologic lesion and it location	36.36	83.15	34.78	84.09
E. not attributed to another disorder	20.72	-	100.00	0.00
Possible PPTTN (criteria A and E)	13.04	94.32	37.50	80.58
Probable PPTTN (criteria A, C or D, and E)	13.04	94.32	37.50	80.58
Definite PPTTN (criteria A, C and D, and E)	39.13	79.55	33.33	83.33

PPV, positive predictive value; NPV, negative predictive value; PPTTN, Peripheral Painful Traumatic Trigeminal Neuropathy.

D. Sensitivity, specificity, PPV, and NPV for outcome predictors and diagnosis

Table 8 provides estimates for sensitivity, specificity, PPV, and NPV for individual variables with significance, and for diagnoses of outcome predictors.

Compared to the results of the PPTTN criteria, this empirical approach with adjustment and in combination with outcome predictors resulted in a profound increment in sensitivity, but also a small decrement in specificity.

We generated an receiver operating characteristic (ROC) curve by plotting the sensitivity of the screener total score against the value of one minus the specificity.[8)]

The items that had an area under the ROC curve (AUC) of more than 0.5 were touch(blunt) radiating, pinprick radiating, and allodynia. Once adjusted and combined with outcome predictors, all variables showed greater than 0.5 AUC except for panoramic view result + radiating after pin stimulus.

Table 8. Sensitivity, specificity, PPV, NPV of each outcome predictor, and diagnoses of adjusted outcome predictors redistributed according to the PPTTN criteria

Outcome predictor (matched to PPTTN criteria)	Sensitivity	Specificity	PPV	NPV
Reduced sensation in the pinprick test (C)	30.44	65.91	18.92	78.38
Radiating after pin stimulus (C)	82.61	56.82	33.33	92.59
Panoramic view result (D)	60.87	63.64	30.44	86.15
Reduced sensation in the pinprick test (C) + Panoramic view result (D)	73.91	36.36	23.29	84.21
Radiating after pin stimulus (C) + Panoramic view result (D)	95.65	36.36	28.21	96.97
Receptive field (A) + Panoramic view result (D)	60.87	60.23	28.57	85.48
Receptive field (A) + Reduced sensation in the pinprick test (C)	39.13	62.50	21.43	79.71
Receptive field (A) + Reduced sensation in the pinprick test (C) + Panoramic view result (D)	69.57	39.77	23.19	83.33

PPV, positive predictive value; NPV, negative predictive value; PPTTN, Peripheral Painful Traumatic Trigeminal Neuropathy.

Ⅳ. Discussion

Recently, traumatic trigeminal neuropathy has been a significant research interest for dentistry.[5,8] It is a major, largely unrecognized clinical problem, which is distressing for and reduces the quality of life of patients.[10]

Therefore, there is need for a consensus and standardization of assessment of traumatic trigeminal neuropathy, while also simultaneously differentiating temporary from permanent injuries caused in the early traumatic event, in order to encourage patients to seek the appropriate interventions. However, there has been no agreed diagnostic method or test to unequivocally show the presence of neuropathic pain thus far. Consequently, it is important for dentists to design the diagnostic criteria, and the treatment protocols for these diagnoses.

In this study, enrolled patients were grouped according to duration of symptoms, with the critical time set at 3 months. Defining the time at which permanent nerve injury is diagnosed might be performed differently by different authors. In most previous articles, injuries were regarded as permanent if the patient had symptoms for more than 6 months, because paresthesia was found to be temporary, and tended to subside within the first 6 months.[5,11-13] Based on these studies, clinicians have a tendency to instruct patients who show signs of nerve damage to wait at least six months. However, full recovery of nerve function is less likely when the patient is seen a long time after a severe injury.[5] Furthermore, proposing the PPTTN criteria defined as PPTTN as having continued symptoms for 3 months. This was in line with a recent review article that posited that after 3 months, permanent central and peripheral changes occur within the nervous system subsequent to injury that are unlikely to respond to surgical intervention.[10,14] Furthermore, it is important to differentiate neuropathic from non-neuropathic causes for the diagnosis and treatment

of the conditions. A key feature of neuropathic pain is the combination of sensory loss with paradoxical hypersensitivity. Damage to the afferent transmission system causes partial or complete loss of input to the nervous system, leading to negative sensory phenomena, such as loss of touch or temperature or pressure sensations.[13] In contrast, inflammatory pain heightens pain sensitivity in response to tissue injury and inflammation, and it is also associated with hypersensitivity to normal sensory inputs.[10] Accordingly, symptoms that occurred for less than 3 months could originate from either inflammatory or neuropathic conditions. Therefore, defining the time between transient and persistent neuropathy as 3 months in this study seemed most appropriate.

In this study, most patients (84 out of 111, 75.67%) had neuropathic pain, while only 17 patients had lowered or completely numb sensation without pain. It is known that approximately 35% of chronic pain patients suffer from neuropathic pain.[5] Following the injury to trigeminal nerve branches, chronic pain develops in about 3-5% of patients.[6,15] These symptoms coupled with neuropathic pain could be especially troublesome to patients, and result in a severe reduction of their overall quality of life.

The distributions of initiating events affecting altered sensation or pain are summarized in Table 2. Injury to the trigeminal nerve may occur from a variety of different dental treatments, including third molar extraction,[16] implant placement,[17,18] dental local anesthetic injection,[19] endodontic treatment,[20] and orthognathic surgery.[21] Non-iatrogenic causes such as skull fracture could also result in considerable nerve injury. In this study, implant placement caused the highest incidence of trigeminal nerve injuries (27.93%). In contrast, previous studies state that third molar extraction caused the highest incidence of iatrogenic trigeminal nerve injuries,[9,22] which was the second most common cause in this study (22.52%). Local anesthetic-related injury was only 2.70% of the incidence in this study. The difference could be explained by the fact that neuropathy related to third molar extraction or local anesthetic injection is usually temporary,[23]

and thus patients do not seek secondary or tertiary referrals. Notably, some patients develop chronic neuropathic pain following negligible nerve trauma such as suturing of wounds, operative dental treatment, and periodontic treatment.

In the comparison of patient profiles, the presence of a neurologic lesion in the panoramic view result, reduced sensation and radiation in the pinprick test, radiating sensation with the blunt stimulus, and allodynia showed differences between the transient and persistent groups (Table. 6). According to the result of the multiple regression analysis, the presence of a neurologic lesion in panoramic view result and reduced sensation and radiating symptoms in the pinprick test would be defining features of one of the main clinical features of persistent neuropathy. Most patients with delayed visits complained that their doctor had advised them to wait and see, without any attempt to relieve their symptoms. Fast referral fast to a specialist in orofacial pain or oral surgery may help maximize the resolution of neuropathy, by interrupting and reversing the cascade of traumatic events.[5,24] Many authors recommend the referral of injuries before 4 months but this may be too late for many peripheral sensory nerve injuries,[5] since the first few months may determine the degree of nerve healing.[4] This time would need to be very short, perhaps within 24 hours of the injury, in the cases of implant or endodontic-related injury.[20,25] Therefore, identifying risk factors affecting permanent neuropathy would help clinicians to refer patients with neuropathic symptoms at the best possible time.

The panoramic view could provide gross information on involvement of inferior alveolar nerve injury (IANI), demonstrating the loss of the lamina dura of the IAN canal, impingement of implant fixtures, and overfilling of endodontic materials into the IAN canal. However, in the case of lingual nerve injury (LNI), and sometimes of mental nerve injury (MNI), the panoramic view does not provide proper information regarding nerve damage. Conebeam CT (CBCT) scanning might be an alternative option,[26]

but several papers have reported the weakness of CBCT evaluation in identifying the canal, resulting in poorer sensitivity and specificity.[27,28] In this study, however, there were 14 positive signs of nerve damage in CBCT, while there were 46 cases of no sign in the panoramic view. Thus, using CBCT may not be a routine procedure to assess the extent of nerve damage, but it could be necessary if the panoramic image fails to detect signs of nerve damage.

If a nerve injury is suspected, the clinician should perform a basic neurosensory examination of the neuropathic area and ascertain whether or not the patient is experiencing pain, altered sensation, or numbness.[4] In this study, reduced sensation in the pinprick test (hypoalgesia) was statistically significantly more frequent in the persistent group than in the transient group. Sensory loss is a universal response to nerve damage,[10] but hypoalgesia, in assessing sensory signature, was not predominant in the persistent group. In the comparison about sensory signature, allodynia showed statistically significance in the persistent group, compared to the transient group (Table 5). After the nerve injury, reactive changes centrally produce abnormal neural function. Allodynia (pain evoked by innocuous stimuli), and hyperpathia (anexplosive, abnormal pain that outlasts a stimulus) would indicate altered activity of peripheral nerves and their central pathway.[4] Therefore, a combination of dull sensation, allodynic and hyperpathic responses in a neurosensory examination could serve as an outcome predictor for the likelihood of permanent neuropathy. In this study, Nagelkerke's R^2, which represents the power of explanation of the model,[29] was 0.607. As scores of Nagelkerke's R^2 above 0.5 would indicate a strong association with the group.[30] Our value of 0.607 is indicatative of a strong association with the persistent group. To our knowledge, this is the first study to assess the difference in patient profiles between the transient and persistent groups. Based on this study, further investigations with larger study populations are warranted.

Application of PPTTN criteria in this study provided low sensitivity and

PPV, but relatively high specificity and NPV. The result of this study confirms that PPTTN criteria would be clinically applicable, but would not yet be a gold standard for evaluation of traumatic trigeminal neuropathy. Therefore, we took an empirical approach using adjustment and combinations with outcome predictor. Compared to the results of the PPTTN criteria, this approach generated a profound increment in sensitivity, but with a small decrement in specificity. However, all variables adjusted and combined with outcome predictors except for panoramic view result + radiating after pin stimulus showed more than 0.5 AUC. The area under the ROC curve (AUC) is a measure of the correlation between the prediction of the screener and the gold standard diagnosis. Because an AUC score above 0.5 represents low to moderate accuracy (and high accuracy if above 0.9),[31] our results indicated that these features could improve PPTTN criteria in terms of sensitivity and specificity. However, application of them to this study population produced good specificity and low sensitivity. Therefore, these outcome predictors could serve as a screening tool, but not as a diagnostic criteria. On the other hand, the use of this screening tool might represent an important step toward effective treatment and realistic expectations for patients. Further study will be needed with larger sample, and multi-center design, such as headache validation study.[32]

An ideal model for studying the development of chronic traumatic neuropathic pain, and establishing predictive factors for the condition, would include preoperative and postoperative assessment of psychological and neurophysiological factors, detailed intraoperative data on handling of tissue and nerves, and detailed early and late postoperative pain data, as well as a thorough clinical investigation to exclude other causes of the chronic pain state.[10] In this study, psychological evaluation was not performed. Considering the risk factors for postsurgical pain, psychological evaluation should be included in future studies.

Ⅴ. Conclusions

1. The presence of a neurologic lesion in panoramic view result and reduced sensation and radiating symptoms in the pin prick test would be defining features of one of the main clinical features of persistent neuropathy. These features could serve as outcome predictors diagnosing the permanent nerve injury in trigeminal nerve.

2. Application of PPTTN criteria in this study showed low sensitivity and positive predictive value (PPV), but sensitivity and negative predictive value (NPV) were relatively high. PPTTN criteria would be clinically applicable, but they might not yet be a gold standard for evaluation of traumatic trigeminal neupathy as it is.

3. Compared to the results of the PPTTN criteria, an empirical approach using adjustment and combinations with outcome predictor generated a profound increment in sensitivity, but with a small decrement in specificity. Therefore, these outcome predictors could serve as a screening tool, but not as a diagnostic criteria. Further study will be needed with larger sample, and multi-center design

References

1. Woda A. Painful posttraumatic trigeminal neuropathy: a recently recognized entity. J Orofac Pain. 2013;27(2):97-98.

2. Ryu JW, Gwon JS. Dysesthesia after tooth extraction and implant surgery reported by dentists. Korean J Oral Med. 2007;32(3):263-272.

3. Merrill RG. Prevention, treatment, and prognosis for nerve injury related to the difficult impaction. Dent Clin North Am. 1979;23(3):471-488.

4. Renton T. Prevention of iatrogenic inferior alveolar nerve injuries in relation to dental procedures. Dent Update. 2010;37(6):350-363.

5. Renton T, Yilmaz Z. Profiling of patients presenting with posttraumatic neuropathy of the trigeminal nerve. J Orofac Pain. 2011;25(4):333-344.

6. Benoliel R, Zadik Y, Eliav E, Sharav Y. Peripheral painful traumatic trigeminal neuropathy: clinical features in 91 cases and proposal of novel diagnostic criteria. J Orofac Pain. 2012;26(1):49-58.

7. Park JW, Choung PH, Kho HS, Kim YK, Chung JW. A comparison of neurosensory alteration and recovery pattern among different types of orthognathic surgeries using the current perception threshold. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111(1):24-33.

8. Kraemer H. Evaluating medical tests. Objective and quantitative guidelines. Thousand Oaks, CA: Sage Publications, 1992.

9. Hillerup S. Iatrogenic injury to the inferior alveolar nerve: etiology, signs and symptoms, and observations on recovery. Int J Oral Maxillofac Surg. 2008;37(8):704-709.

10. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-1625.

11. Jerjes W, Swinson B, Moles DR, et al. Permanent sensory nerve impairment following third molar surgery: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102(4):e1-7.

12. Osborn TP, Frederickson G Jr, Small IA, Torgerson TS. A prospective study of complications related to mandibular third molar surgery. J Oral Maxillofac Surg. 1985;43(10):767-769.
13. Wofford DT, Miller RI. Prospective study of dysesthesia following odontectomy of impacted mandibular third molars. J Oral Maxillofac Surg. 1987;45(1):15-19.
14. Ziccardi VB, Steinberg MJ. Timing of trigeminal nerve microsurgery: a review of the literature. J Oral Maxillofac Surg. 2007;65(7):1341-1345.
15. Benoliel R, Birenboim R, Regev E, Eliav E. Neurosensory changes in the infraorbital nerve following zygomatic fractures. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99(6):657-665.
16. Mason DA. Lingual nerve damage following lower third molar surgery. Int J Oral Maxillofac Surg. 1988;17(5):290-294.
17. Wismeijer D, van Waas MA, Vermeeren JI, Kalk W. Patients' perception of sensory disturbances of the mental nerve before and after implant surgery: a prospective study of 110 patients. Br J Oral Maxillofac Surg. 1997;35(4):254-259.
18. Kraut RA, Chahal O. Management of patients with trigeminal nerve injuries after mandibular implant placement. J Am Dent Assoc. 2002;133(10):1351-1354.
19. Hillerup S, Jensen R. Nerve injury caused by mandibular block analgesia. Int J Oral Maxillofac Surg. 2006;35(5):437-443.
20. Grötz KA, Al-Nawas B, de Aguiar EG, Schulz A, Wagner W. Treatment of injuries to the inferior alveolar nerve after endodontic procedures. Clin Oral Investig. 1998;2(2):73-76.
21. Jääskeläinen SK, Teerijoki-Oksa T, Virtanen A, Tenovuo O, Forssell H. Sensory regeneration following intraoperatively verified trigeminal nerve injury. Neurology. 2004;62(11):1951-1957.
22. Bataineh AB. Sensory nerve impairment following mandibular third molar surgery. J Oral Maxillofac Surg. 2001;59(9):1012-1017.
23. Hillerup S. Iatrogenic injury to oral branches of the trigeminal nerve:

records of 449 cases. Clin Oral Investig. 2007;11(2):133-142.
24. Susarla SM, Lam NP, Donoff RB, Kaban LB, Dodson TB. A comparison of patient satisfaction and objective assessment of neurosensory function after trigeminal nerve repair. J Oral Maxillofac Surg. 2005;63(8):1138-1144.
25. Khawaja N, Renton T. Case studies on implant removal influencing the resolution of inferior alveolar nerve injury. Br Dent J. 2009;206(7):365-370.
26. Friedland B, Donoff B, Dodson TB. The use of 3-dimensional reconstructions to evaluate the anatomic relationship of the mandibular canal and impacted mandibular third molars. J Oral Maxillofac Surg. 2008;66(8):1678-1685.
27. Tantanapornkul W, Okouchi K, Fujiwara Y, et al. A comparative study of cone-beam computed tomography and conventional panoramic radiography in assessing the topographic relationship between the mandibular canal and impacted third molars. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(2):253-259.
28. Tantanapornkul W, Okochi K, Bhakdinaronk A, Ohbayashi N, Kurabayashi T. Correlation of darkening of impacted mandibular third molar root on digital panoramic images with cone beam computed tomography findings. Dentomaxillofac Radiol. 2009;38(1):11-16.
29. Pace NL, Eberhart LH, Kranke PR. Quantifying prognosis with risk predictions. Eur J Anaesthesiol. 2012;29(1):7-16.
30. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev Vet Med. 2000 May;45(1-2):23-41.
31. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev Vet Med 2000;45:23-41.
32. Lipton RB, Dodick D, Sadovsky R et al. A self-administered screener for migraine in primary care: The ID Migraine validation study.

Neurology. 2003;61(3):375-382.