Thermal Perception as a Key Factor for Assessing Effects of Trigeminal Nerve Injury

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Aims: To conduct a functional examination using multimodal exploration of a sample of patients with iatrogenic trigeminal nerve injury to understand the underlying mechanisms of neuropathic pain following trigeminal nerve injury. **Methods:** Subjective and objective symptoms and responses to thermal and electrical quantitative sensory testing (QST) were evaluated in 85 patients with unilateral trigeminal nerve injury. Objective symptoms were measured by seven clinical sensory tests. Thermal QST included cold detection threshold (CDT), warm detection threshold (WDT), and heat pain threshold (HPT). Electrical current perception threshold was performed with electrical stimuli of 2,000, 250, and 5 Hz. The time since injury was included as a possible independent variable. The data were analyzed using chi-square test, independent *t* test, Mann Whitney *U* test, one-way analysis of variance (ANOVA), and Kruskal-Wallis test. Further analyses with Pearson correlation analysis, Spearman rank correlation analysis, and cluster analysis were applied. **Results:** Unlike objective symptoms, thermal and electrical QST values and subjective symptoms did not improve in patients with an old injury. Thermal QST, particularly WDT, showed the highest positive correlation with subjective symptoms in all tests. Cluster analysis of the thermal QST values identified three subgroups: cluster 1, which was characterized by prominent cold and warm hypoesthesia; cluster 2, which presented elevated WDT; and cluster 3, which showed the smallest thermal differences for all thermal variables but had the highest proportion of neuropathic pain. **Conclusion:** These findings have demonstrated that thermal QST is a suitable tool for evaluating and characterizing the sensory effects of trigeminal nerve injury. Three subgroups with different thermosensory profiles showed that the less the damage, the more neuropathic pain occurs. The loss of warm perception in particular might play a pivotal role in the chronicity and severity of subjective sensory symptoms. *J Oral Facial Pain Headache 2017;31:129–138. doi: 10.11607/ofph.1732*

Keywords: *prognosis, thermal, trigeminal nerve injury, quantitative sensory testing, warm*

Injury to the trigeminal nerve is a well-known but unwanted complication of invasive dental treatments that may cause unremitting pain as well as compromised sensation in the orofacial region. Nerve damage in the trigeminal region commonly causes a debilitating loss of daily functions related to speech, eating, tooth brushing, kissing, drinking, shaving, tasting, and confidence.[1] Profound effects on quality of life as well as unremitting neurosensory malfunctions are often sufficient for patients to bring malpractice suits, and so it is necessary for clinicians to make every effort to avoid nerve injury. Although accidental iatrogenic trigeminal nerve injury is not common,[2,3] clinicians who perform oral surgery can hardly be free from causing some nerve damage. Thus, an accurate assessment of nerve damage is a crucial matter for all clinicians.

Trigeminal nerve injury is well recognized for its heterogenous profiles of sensory dysfunction between patients even after identical injuries due to probable neuronal plasticity.[4,5] In addition, some patients with a relatively mild injury such as nerve compression reported sustained sensory abnormalities similar to those of patients with more serious injuries such as nerve transection.[6] These findings indicate that

the diagnosis of nerve damage and accompanying neuropathic pain is no simple task. Thus, there has been great effort to evaluate and analyze the clinical and neurosensory characteristics of patients with trigeminal nerve damage.

In 1992, Zuniga and Essick[7] presented the first working guidelines for the evaluation and diagnosis of trigeminal nerve injury for clinicians. They recommended three steps: patient report, physical examination, and clinical sensory testing. However, clinical sensory testing is not enough for the accurate diagnosis of nerve injury due to its lack of reliability and quantification. Therefore, neurophysiologic and psychophysical quantitative sensory testing (QST) was introduced for the diagnosis of peripheral nerve injury.[8–13] The German Research Network on Neuropathic Pain (DFNS) reported a standardized protocol for and reference values of 13 QST measures.[14] QST is seemingly more reliable and accurate, and thermal QST has been especially recognized as an essential and valid tool in the evaluation of sensory nerve injury.[15–17]

To date, there are many previous reports using thermal QST for sensory profiles of patients with trigeminal nerve injury.[9,18–21] However, to the best of the authors' knowledge, no study has described the characteristics of patients with iatrogenic trigeminal nerve injury by using thermal and electrical QST as well as subjective and objective symptoms. Therefore, the aim of the present study was to conduct a functional examination using multimodal exploration of a sample of patients with iatrogenic trigeminal nerve injury to understand the underlying mechanisms of neuropathic pain following trigeminal nerve injury.

Materials and Methods

Subjects

The study included 90 patients who consecutively presented from March 2011 to March 2015 to the Department of Oral Medicine at the Dankook University Dental Hospital with a complaint of abnormal sensation, including numbness and pain, in the orofacial region. All of the patients presented a history of unilateral nerve injury related to dental etiologies in the orofacial region. Four specialists (H.K.K.; G.H.L.; K.S.K.; M.E.K.) in temporomandibular disorder (TMD) and orofacial pain diagnosed peripheral nerve neuropathy resulting from trigeminal nerve injury after history taking and clinical examination. To be eligible for inclusion, subjects *(1)* had to have a history of acute onset of sensory deficits or abnormalities, *(2)* had to undergo at least thermal and electrical QST, and *(3)* did not have any neurologic disease or relevant systemic disease with a high risk of peripheral nerve neuropathy. The study was approved by the Institutional Review Board committee of Dankook University Dental Hospital (IRB No. H-1503/003/005). Informed consent was obtained from all participants on the day of their first visit to the Dankook University Dental Hospital.

Clinical Examination

Information about the time from the injury to the first consultation and the patients' subjective ratings of their quantitative sensory state (sensory gain or loss) and qualitative sensory discomforts (paresthesia and dysesthesia) were retrospectively obtained from medical records. All tests were limited to the mentum, tongue, and cheek. The unaffected side contralateral to the nerve injury served as a control. Psychophysical testing was performed by one experienced specialist in TMD and orofacial pain (H.K.K) in all patients except six cases.

Subjective Symptoms

The patients were asked to rate their sensory function of the symptomatic sites quantitatively and qualitatively on a numeric rating scale (NRS) with endpoints 0 indicating no sensory abnormality and 10 indicating worst discomfort imaginable. The patients were asked to rate their symptoms compared to the unaffected side. The quantitative sensory function could reflect hypoesthesia related to sensory loss or hyperesthesia related to sensory gain. Qualitative ratings of neurosensory symptoms consisted of nine aspects: tingling, pricking, shooting, burning, dull, tightness, numbness, swelling, and itch. The overall subjective symptoms (range from 0–110) of sensory dysfunction were expressed through the sum scores of quantitative ratings (range from 0–20) and qualitative ratings (range from 0–90); that is, a score of 0 denoted normal perception and a score of 110 denoted the worst neurosensory dysfunction.

Objective Symptoms

Clinical sensory testing of objective symptoms (brush stroke, pinprick, sharp-blunt discrimination, stimulus localization, brush stroke direction, pressure, two-point discrimination) was carried out in the patients to evaluate sensory function. The patients were asked to use a 10-point NRS[1] to grade the level of sensory perception of the affected side in comparison to that of the unaffected side for brush stroke, pinprick, sharp-blunt discrimination, and pressure stimuli. If patients had hypersensitivity or hyperalgesia, they were instructed to rate this from 10 to 20. The tests were carried out as follows:

- Brush stroke: A cotton swab was gently brushed against the skin (0 = no perception of touch and brush, 10 = normal perception).
- Pinprick: A dental probe with a sharp tip

was gently pressed on the test site so as to indent the skin without piercing it, and the patients were requested to rate the perception (0 = no perception of pinprick stimuli, 10 = normal perception).
- Sharp-blunt discrimination: The sharp, pointed tip of a dental probe was applied to the site and the patients were requested to rate the sharpness of the stimulus (0 = no sharpness, 10 = normal sharpness).
- Stimulus localization: The pointed tip of a dental probe was applied to five contact points in random order. After each stimulus application, the patients were requested to pinpoint the exact same point. The scores were graded as the number of correct responses (0 to 5).
- Direction discrimination: Five moving brush strokes, applied with the back of a dental mirror, were applied randomly by the examiner. After each stimulus, the patients were asked to duplicate the direction with a finger. The scores were graded as the number of correct responses (0 to 5).
- Pressure: The index finger of the examiner was pressed against the test sites so as to indent the skin with mild to moderate discomfort as rated by the patient (0 = no perception of pressure, 10 = normal perception).
- Two-point discrimination: A compass with a blunt tip was employed and the threshold ratio was calculated as the value of the discrimination threshold on the affected side divided by the value on the unaffected side. The ratio was graded as three scores: score 10 for the ratio range 1 ≤ 2; score 5 for the ratio 2 ≤ 3; and score 0 for the ratio ≥ 3.

The level of objective symptoms indicating neurosensory function was characterized as the sum scores of seven components with a range from 0 to 60 (0 = complete loss of neurosensory function, 60 = normal neurosensory function).

QST

The psychophysical tests using QST consisted of two parts. Thermal tests were done first, followed by electrical QST. All patients were tested first on the unaffected side followed by the affected side. The tests were conducted in the center of the hypoesthesia, and in patients with only hyperesthesia, in the center of the hyperesthesia. When lingual nerve injury was suspected, the function of the chorda tympani nerve was examined by using an electrogustometry device. The data on the electrical taste thresholds for the evaluation of the chorda tympani nerve were not included in this study.

Thermal QST

Thermal QST was performed in the patients in the same manner as the method described in detail in a previously published article.[22] A TSA II (Medoc, Israel) thermal sensory analyzer was used to measure in order cold detection threshold (CDT), warm detection threshold (WDT), and heat pain threshold (HPT) by the method of limits technique. Cold pain threshold (CPT) was not assessed due to its high variability.[22] The contact area of the thermode was 5 × 5 mm for the intraoral area (tongue mucosa) as well as for the extraoral skin. The baseline temperature was set at 32°C for extraoral sites and 36°C for the tongue because the surface temperature differs between intraoral and extraoral tissues, and the baseline temperature should be perceived as neutral. Cut-off temperatures were 0°C for cold stimuli and 50°C for warm and hot stimuli. Thermal QST results were transformed to between-side (between affected side and contralateral side) differences (CDT [%], WDT [%], HPT [%]) to present between-individual variability. They were then further divided by the unaffected side value to reduce inter-individual variability and were expressed as percentages.

Electrical Current Perception

Standardized electrical current perception threshold (CPT) tests using a Neurometer CPT/C device were performed bilaterally by the double-blinded, forced-choice mode and with electrical stimuli of 2,000, 250, and 5 Hz in extraoral regions such as the mentum and upper lip of the patients. Similar to thermal QST, the between-side differences divided by the unaffected side value were calculated for further analyses and expressed as a percentage (2,000 Hz [%], 250 Hz [%], 5 Hz [%]).

Data Analyses

The normality of the data was checked by using the Kolmogorov-Smirnov test and the nonparametric test was applied when data were not normally distributed.

For all descriptive variables, the mean and standard deviation (SD) or median and interquartile range (IQR) were calculated. The chi-square test was performed to compare the frequency and distribution of the relevant nerve branches and etiology of the injury among the patients. The patients were categorized into two groups according to the time since injury, with two cut-off points of 3 and 6 months. Independent *t* test and Mann-Whitney *U* test were performed to compare the scores of the objective symptoms and psychophysical testing between the different groups according to the time since injury. Pearson's correlation analysis was performed to assess the association between subjective and objective symptoms, as well as associations with age and the time since injury. Correlations between subjective symptoms

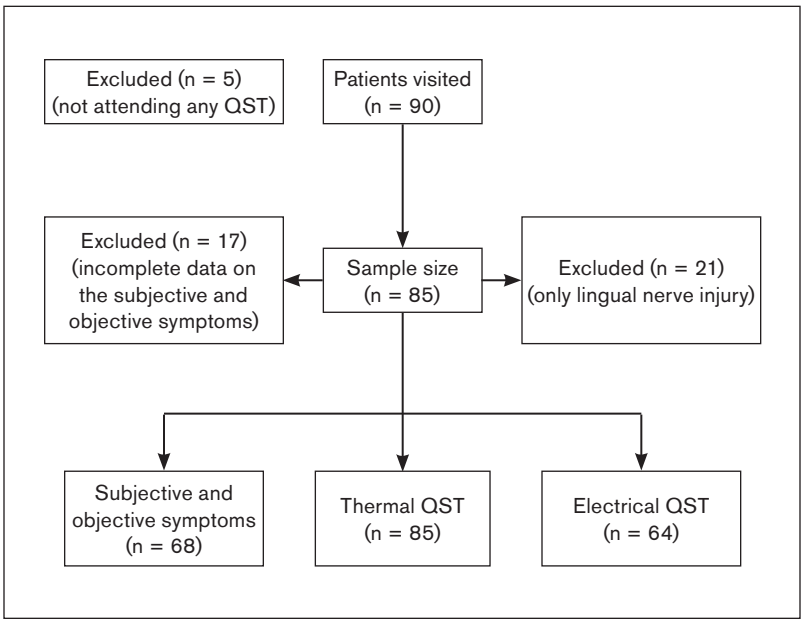

Fig 1 Study sample flowchart. QST = quantitative sensory testing.

Table 1 Etiology and Related Nerve Branches of 85 Patients with Trigeminal Neuropathy

	Etiology					*P*
Nerve branch	Extraction	Implant	Injection	Endodontic	Other[b]	value[c]
Inferior alveolar nerve (n = 63)	13	35	6	4	5	< .001
Mentum (n = 63)	13	35	6	4	5	
Lower lip (n = 63)	13	35	6	4	5	
Teeth (n = 42)	9	22	3	4	4	
Lingual nerve (n = 23)	16	0	7	0	0	< .001
Chorda tympani nerve (n = 16)	12	0	4	0	0	
Infraorbital nerve (n = 1)	0	0	0	0	1	.836
Upper lip	0	0	0	0	1	
Total, n (%)[a]	28 (32.9)	35 (41.2)	12 (14.1)	4 (4.7)	6 (7.1)	85 (100)

[a]Total denotes the frequency (number of eligible subjects who were categorized according to the etiology and related nerve of nerve injury) and percentage of distribution according to the etiology in 85 patients.
[b]Other includes dentoalveolar surgery (n = 6).
[c]*P* value determined from chi-square test.

and the results of the psychophysical testing were analyzed by using Spearman rank correlation analysis. A nonhierarchical cluster analysis with K-means was applied to three thermal threshold scores as an exploratory test in order to identify subgroups with distinct thermal sensory profiles. Before the nonhierarchical clustering, the number of clusters was selected by using hierarchical clustering with Ward's distance. After patients were clustered by resemblance of their thermal QST profiles, Kruskal-Wallis test, one-way analysis of variance (ANOVA), and chi-square test were performed to compare the clinical characteristics among clusters. For post hoc comparison of the nonparametric data, R programming for multiple comparisons was done. Data analyses were completed with Statistical Package for Social Sciences (SPSS for Window, version 21.0, SPSS. Inc), and statistical significance was set at $P \leq .05$.

Results

Demographic and Clinical Characteristics of the Patients

Five patients who had not received any psychophysical tests were excluded, and so 85 patients were included in this study sample. A study sample flowchart is shown in Fig 1. Subjective and objective symptoms of 68 patients were available, 85 patients were evaluated with thermal QST, and 64 patients with electrical QST.

Of the total 85 patients, 49 (47.6%) were female, and the mean age was 45.5 ± 12.9 years. The median time spent from injury to the first consultation was 3 months (IQR from 0.5 to 9, and range from 0.1 to 48 months). The right side was affected in 42 cases and the left side in 43 cases (49.4% and 50.6%, respectively).

Table 1 shows the etiology and the related branches of the trigeminal neuropathy. Implant surgery was the most prevalent cause of the nerve injuries followed by third molar extraction, local anesthetic injury and endodontic procedures, and others. The most commonly related nerve branches were the inferior alveolar nerve, followed by the lingual nerve.

Clinical and Psychophysical Assessments

In the normality test of the data, the total sum scores of subjective symptoms ($P = .200$) and objective symptoms ($P = .063$) showed a normal distribution, while all thermal and electrical QST variables were not normally distributed ($P < .0001$).

All patients showed between-side differences in at least one of the sensory tests as well as in subjective symptoms. In the subjective symptoms, hypoesthesia rather than hyperesthesia was the prevailing neurogenic symptom (Table 2). Of the nine sensory descriptions, numbness was by far the most prevalent complaint, followed in order by swelling, tingling,

Table 2 Baseline Results of Subjective Symptoms (n = 68)

Items	n (%)	Rating (mean ± SD)
Quantity		
Hypoesthesia	60 (88.2)	5.3 ± 2.4
Hyperesthesia	47 (69.1)	3.5 ± 2.0
Σ Quantity[a]		7.1 ± 3.4
Quality		
Tingling	29 (42.6)	2.1 ± 0.9
Pricking	22 (32.4)	4.3 ± 2.2
Shooting	3 (4.4)	8.3 ± 0.3
Burning	21 (30.9)	3.8 ± 1.7
Dull	18 (26.5)	3.5 ± 1.8
Tightness	27 (39.7)	3.7 ± 2.1
Numbness	57 (83.8)	5.3 ± 2.4
Swelling	32 (47.1)	4.6 ± 2.5
Itch	10 (14.7)	2.7 ± 1.2
Σ Quality[b]		13.3 ± 9.8
Σ Subjective symptoms (total)		20.4 ± 12.7

The overall subjective ratings of sensory dysfunction (range from 0–110) were expressed through the sum scores of [a]quantitative ratings (range from 0–20) and [b]qualitative ratings (range from 0–90).

Table 3 Baseline Results of the Objective Symptoms and Psychophysical Tests

Examination	Rating (Median [IQR])
Objective symptoms (n = 68)	
Brush stroke	6 (3.1–9.0)
Pinprick	7.7 (5.0–10.0)
Sharp-blunt discrimination	8 (5.0–10.0)
Stimulus localization	5 (5.0–5.0)
Brush stroke direction	5 (5.0–5.0)
Pressure	7.2 (5.0–10.0)
Two point discrimination	10 (5.0–10.0)
Σ Objective symptoms	49.3 (34.2–58.0)
Thermal QST (°C) (n = 85)	
CDT (%)	0.04 (0.00–0.08)
WDT (%)	0.1 (0.0–0.26)
HPT (%)	0.03 (0.01–0.09)
Σ Thermal QST (%)	0.2 (0.09–0.50)
Electrical QST (mA) (n = 64)	
2,000 Hz (%)	0.8 (0.3–1.9)
250 Hz (%)	0.6 (0.2–2.6)
5 Hz (%)	0.9 (0.2–3.9)
Σ Electrical QST (%)	2.5 (1.1–7.6)

CDT (%), WDT (%), HPT (%), for thermal QST and 2,000 Hz (%), 250 Hz (%), and 5 Hz (%) for electrical QST indicate the between-side differences (the affected side – the unaffected side) divided by the unaffected side value; Σ Objective symptoms = sum score of seven components and could range from 0 to 60; Σ Thermal QST (%) = sum score of CDT (%), WDT (%), and HPT (%); Σ Electrical QST (%) = sum score of 2,000 Hz (%), 250 Hz (%), and 5 Hz (%).

tightness, pricking, burning, dull, itch, and shooting. The median sum score of objective symptoms was 49.3 (out of a total possible score of 60) and brush stroke stimuli presented with the lowest score (Table 3). For thermal QST, the median of thermal differences was highest for WDT (Table 3).

Stratification of Clinical and Psychophysical Test Scores According to Time Since Injury

The cut-off points for categorization of acute and chronic pain were arbitrarily set at 3 and 6 months, respectively. Table 4 shows the scores of subjective symptoms, objective symptoms, and psychophysical tests stratified according to the time since injury. In both categorizations, the sum score of subjective symptoms and the results of psychophysical tests did not differ between groups, unlike the sum score of objective symptoms. The sum score of objective symptoms did not statistically differ between two groups when the cut-off was 3 months (P = .073); however, the group with an injury over 6 months showed significantly improved scores in most objective symptoms.

Table 4 The Effect of Time Since Injury on Subjective Symptoms and the Results ofNeurosensory Tests

	Time since injury		*P* value
	< 6 mo	≥ 6 mo	
Σ Subjective symptoms (n = 68) (Mean ± SD)	n = 43 (21.3 ± 13.0)	n = 25 (18.7 ± 12.1)	.407[a]
Objective symptoms (n = 68), n (mean ± SD)	n = 43	n = 25	
Brush stroke	5.4 ± 3.8	7.8 ± 3.5	.012[a]
Pinprick	6.8 ± 4.0	9.6 ± 4.5	.015[a]
Sharp-blunt discrimination	6.5 ± 3.0	8.3 ± 1.9	.005[a]
Stimulus localization	4.2 ± 1.3	4.8 ± 0.6	.017[a]
Brush stroke direction	4.6 ± 1.1	4.9 ± 0.4	.131[a]
Pressure	6.0 ± 3.0	9.0 ± 3.9	.002[a]
Two-point discrimination	7.0 ± 4.1	8.6 ± 2.7	.074[a]
Σ Objective symptoms	40.8 ± 16.5	53.2 ± 14.0	.002[a]
Thermal QST (°C) (n = 85), Median (IQR)	n = 51	n = 34	
CDT (%)	0.05 (0.01–0.30)	0.03 (0.00–0.07)	.078[b]
WDT (%)	0.10 (0.02–0.29)	0.12 (0.03–0.22)	.986[b]
HPT (%)	0.03 (0.01–0.07)	0.04 (0.01–0.12)	.228[b]
Σ Thermal QST (%)	0.21 (0.08–0.66)	0.22 (0.09–0.41)	.634[b]
Electrical QST (mA) (n = 64) Median (IQR)	n = 37	n = 27	
2,000 Hz (%)	1.13 (0.34–2.57)	0.63 (0.33–0.98)	.072[b]
250 Hz (%)	0.65 (0.22–2.25)	0.64 (0.20–4.57)	.749[b]
5 Hz (%)	1.20 (0.24–3.75)	0.93 (0.29–4.00)	.886[b]
Σ Electrical QST (%)	3.26 (1.54–7.10)	1.79 (1.00–8.14)	.381[b]

CDT (%), WDT (%), HPT (%), for thermal QST and 2,000 Hz (%), 250 Hz (%), and 5 Hz (%) for electrical QST indicate the between-side differences (the affected side – the unaffected side) divided by the unaffected side value; Σ Subjective symptoms = sum score of quantity and quality dimensions in subjective symptoms; Σ Objective symptoms = sum score of seven objective symptoms; Σ Thermal QST (%) = the sum score of CDT (%), WDT (%), and HPT (%); Σ Electrical QST (%) = the sum score of 2000 Hz (%), 250 Hz (%), and 5 Hz (%).
[a]*P* value determined by independent *t* test.
[b]*P* value determined by Mann-Whitney *U* test.

Table 5 Correlation Analyses Between Subjective Symptoms and Clinical Variables, Objective Symptoms, and Psychophysical Tests

	Σ Subjective symptoms	
Variables	Coefficient	*P* value
Age[a]	0.131	.286
Delay since injury[a]	−0.027	.824
Σ Objective symptoms[a]	−0.27	.026
CDT (%)[b]	0.323	.007
WDT (%)[b]	0.504	< .0001
HPT (%)[b]	0.341	.004
Σ Thermal QST (%)[b]	0.519	< .0001
2,000 Hz (%)[b]	0.139	.337
250 Hz (%)[b]	0.157	.277
5 Hz (%)[b]	0.281	.048
Σ Electrical QST (%)[b]	0.286	.044

CDT (%), WDT (%), HPT (%), for thermal QST and 2,000 Hz (%), 250 Hz (%), and 5 Hz (%) for electrical QST indicate the between-side differences (the affected side – the unaffected side) divided by the unaffected side value; Σ Subjective symptoms = sum score of quantity and quality dimensions in subjective symptoms; Σ Objective symptoms = sum score of seven objective symptoms; Σ Thermal QST (%) = the sum of CDT (%), WDT (%), and HPT (%); Σ Electrical QST (%) = the sum of 2,000 Hz (%), 250 Hz (%), and 5 Hz (%).
[a]*P* value and coefficient determined by Pearson's correlation analysis.
[b]*P* value and coefficient determined by Spearman's rank correlation analysis.

Table 6 Thermal Sensory Profiles of the Three Subgroups Clustered by Their Thermal Perception

Group (n = 85)	CDT (%) Median (IQR)	WDT (%) Median (IQR)	HPT (%) Median (IQR)
Cluster 1 (n = 10)	1.00 (1.00–1.00)	0.44 (0.28–0.51)	0.03 (0.02–0.15)
Cluster 2 (n = 22)	0.08 (0.04–0.24)	0.29 (0.23–0.37)	0.07 (0.02–0.13)
Cluster 3 (n = 53)	0.02 (0.00–0.05)	0.05 (0.01–0.10)	0.02 (0.01–0.07)
P value[a]	< .0001	< .0001	.013

CDT (%), WDT (%), and HPT (%) indicate the between-side thermal differences (the affected side – the unaffected side) divided by the unaffected side value; IQR = interquartile range.
[a]*P* value determined by Kruskal-Wallis test.

For the psychophysical testing, between-side differences in WDT did not reveal any statistical significance regardless of cut-off point (3 months, $P = .211$; 6 months, $P = .986$). However, the statistical significance of between-side differences in CDT improved at the cut-off point of 6 months ($P = .078$) compared to 3 months ($P = .951$).

Correlation Analyses Between Subjective and Objective Symptoms, and Psychophysical Tests

Pearson's correlation analysis revealed a mild negative relationship between the sum scores of subjective symptoms and objective symptoms (Table 5). Age and time since injury did not show any significant correlation with the subjective symptoms. In the Spearman's rank correlation analysis, CDT (%) and HPT (%) showed a mild relationship with the subjective symptoms, and WDT (%) exhibited the highest correlation with subjective symptoms among the neurosensory modalities in the current study. Unlike objective symptoms and thermal QST, electrical QST at three different sensory modalities (except for 5 Hz) was not associated with subjective symptoms, but the sum scores of electrical QST (%) showed a mild correlation with subjective symptoms. Of the three different neurosensory modalities, the sum score of thermal QST showed the highest correlation with subjective symptoms.

Cluster Analysis According to the Thermal QST Data

For the thermal QST data, cluster analysis was undertaken to categorize the 85 patients according to their thermal sensory profiles, and this yielded three subgroups. Table 6 reveals that cluster 1 was characterized by prominent cold and warm detection differences higher than the other clusters, whereas cluster 2 showed a prominent between-side difference in WDT. Cluster 3 occupied the majority of the thermal profiles of patients with trigeminal nerve injury and showed the least differences for all thermal variables. Although HPT (%) showed statistical significance between clusters in the Kruskal-Wallis test, multiple comparisons by using R programming for post hoc analysis revealed no significant differences (Fig 2).

Clinical Characteristics According to the Thermosensory Clusters

Table 7 shows that the sum score of subjective symptoms was high in (in order) cluster 1, cluster 2, and cluster 3, but this difference did not reach statistical significance ($P = .072$). On the other hand, the sum scores of objective symptoms were statistically different among the clusters, and the score was high (in order) in cluster 3, cluster 2, and cluster 1. Combined hypoesthesia and hyperesthesia type accounted for the majority of all clusters. Three clusters also showed significantly different sensory type ($P = .043$): that is, the category of anesthesia was seen only in clusters 1 and 2. The proportion of hyperesthesia and coexistence of hypoesthesia and hyperesthesia was the highest in cluster 3.

Discussion

This study aimed to characterize and compare the clinical and psychophysical profiles of patients with posttraumatic trigeminal nerve injury. The main

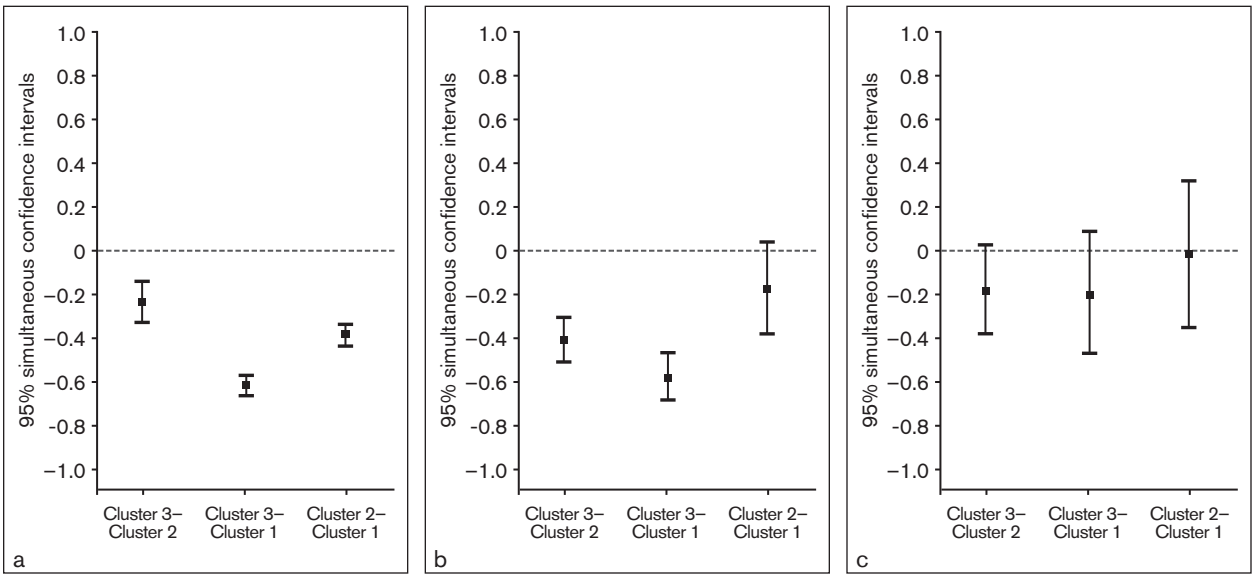

Fig 2 Multiple comparisons using R programming revealed the order of magnitude in the three clusters according to each thermal variable. Tukey method. **(a)** CDT (%): Cluster 1 > Cluster 2 > Cluster 3; Fisher's exact test with 8 degrees of freedom; **(b)** WDT (%): Cluster 1, 2 > Cluster 3; Fisher's exact test with 8 degrees of freedom; **(c)** HPT (%): No differences between the clusters; Fisher's exact test with 11 degrees of freedom.

findings of this study were that most objective symptoms, unlike subjective symptoms and the results of psychophysical testing, were significantly improved in injuries older than 6 months; that thermal QST showed the highest correlation with subjective symptoms among the neurosensory tests used in this study, and in particular a between-side difference in WDT was correlated with subjective sensory perception; and that cluster analysis in the thermal QST values identified three subgroups: cluster 1, which was characterized by prominent cold and warm hypoesthesia, cluster 2, which presented elevated WDT, and cluster 3, which showed the least thermal differences for all the thermal variables but had the highest proportion of neuropathic pain.

Table 7 Comparison of Clinical Characteristics According to the Thermosensory Clusters (n = 68)

Variables	Cluster 1 (n = 9)	Cluster 2 (n = 16)	Cluster 3 (n = 43)	*P* value[b]
Σ Subjective symptoms (mean ± SD)	29.1 ± 15.5	20.9 ± 7.5	18.5 ± 13.1	.072[b]
Quantity	9.3 ± 3.7	7.3 ± 1.8	6.6 ± 3.7	.110[b]
Quality	19.8 ± 12.3	13.6 ± 7.1	11.8 ± 9.8	.084[b]
Σ Objective symptoms (mean ± SD)	29.9 ± 25.6	36.9 ± 10.8	51.8 ± 12.6	< .001[b]
Sensory type,[a] n (%)				
Anesthesia (n = 3)	2 (22.2)	1 (6.3)	0 (0.0)	.043[c]
Hypoesthesia (n = 18)	3 (33.3)	5 (31.3)	10 (23.3)	
Hyperesthesia (n = 9)	1 (11.1)	0 (0.0)	8 (18.6)	
Combined (n = 38)	3 (33.3)	10 (62.5)	25 (58.1)	

Σ Subjective symptoms = sum score of quantity and quality dimensions in subjective symptoms; Σ Objective symptoms = sum score of seven objective symptoms; Combined = indicates coexistence of hypoesthesia and hyperesthesia.
[a]Terminology from Benoliel and Eliav.[4]
[b]*P* value determined by one-way ANOVA.
[c]*P* value determined by chi-square test.

Both patients and clinicians are especially concerned about whether nerve injury will be temporary or permanent. Most temporary nerve injuries are mainly ascribed to compression injury, and recovery of sensation in the majority of patients with compression injuries occurs within 4 to 6 months.[6] Although a prospective study design might be a clear approach to examine the above problem, within the limitations of this cross-sectional study, the authors compared the characteristics between the acute and chronic groups categorized according to the time since the injury and hypothesized that the clinical and psychophysical profiles between the two groups would provide an insight into the pathophysiology of permanent injury.

It is interesting that objective symptoms in this study improved for old injuries in contrast to subjective symptoms and psychophysical test values. In a study by Jääskeläinen et al, clinical sensory tests revealed lower sensitivity to sensory abnormalities than to thermal QST in patients with subjective sensory deficits within the inferior alveolar and lingual nerve distributions.[12] Zuniga et al tested the accuracy of the clinical sensory

test by using surgical findings as a gold standard and reported that the bedside test may result in false negative findings.[23] Although the sum score of objective symptoms showed mild correlation with subjective symptoms in the present study, the discrepancy between subjective and objective symptoms suggests that the improved scores of the clinical sensory tests might not verify subjective symptoms of patients with an old injury. The seven components of the clinical sensory testing in this study can be categorized into two sensory dimensions: mechanoception for the brush stroke, stimulus localization, brush stroke direction, and two-point discrimination tests; and nociception for the pinprick, sharp-blunt discrimination, and pressure tests. These two dimensions showed a strong positive correlation with each other. This finding indicates that the components of clinical testing may not discriminate different sensory profiles very well, and so are not suitable for assessing multiple sensory dimensions.

In line with previous observations in postsurgical studies,[24–27] thermal detection hypoesthesia was also characteristic of the patients in the present study. In thermal QST, the between-side differences of CDT improved for injuries over 6 months (although it did not reach statistical significance) unlike at the cutoff point of 3 months, while warm and heat perceptions were not significantly associated with the time from injury. Dualé et al examined 73 patients at their discharge from hospital and 4 months after pneumonectomy under thoracotomy and found elevated thresholds to warm and heat stimuli on the operated side.[25] Gottrup et al conducted a psychophysical test in 15 patients with pain and 11 patients without pain after breast cancer surgery and showed significantly higher detection thresholds to thermal stimuli on the operated side in both groups. Among the 15 patients with pain, 14 had pain lasting from immediately to 6 weeks postsurgery, and only 1 patient presented symptoms with hypoesthesia to warm rather than cold stimuli over 3 years.[27] An observational study of patients with posttraumatic trigeminal nerve injury revealed that the sensory recovery proceeds in an orderly fashion; ie, the brush-directional discrimination is most rapid, followed by pain thresholds for thermal and mechanical stimuli, touch, two-point discrimination, and CDT.[28] The slowest rate of recovery was seen in WDT.[29] These studies support the findings of the present study.

The vulnerability of warm perception to peripheral nerve injury has been reported in previous studies.[30–34] It was suggested that differences in the recovery rate in different sensory modalities was determined mainly by their relative dependence on functional innervation density.[17,28] The low and variable distribution of warm receptors as compared with the denser and more generalized distribution of cold receptors has been earlier documented,[35] and the physiologic characteristics of warm and cold receptors may be sufficient to explain the results of this study. The high between-side differences in WDT rather than CDT in the patients with chronic injury in this study suggest that the small unmyelinated C-fibers are more vulnerable to permanent nerve injury than the myelinated A-delta fibers, and this might be a negative prognostic factor for recovery. In a study by Vilholm et al, damage to warm sensation was particularly related to neuropathic pain in the patient who had surgery for breast cancer.[26] In line with the previous evidence, the high correlation between the between-side difference of WDT and self-rating for abnormal sensory perception supports the theory that warm perception might be the most valid tool for the evaluation of persistent subjective sensory discomfort.

Like thermal QST values, electrical QST values did not differ between the 3-month and 6-month groups. Interestingly, the between-side differences in electrical QST, except for the stimuli of 5 Hz, did not reveal any relationship to subjective symptoms, unlike thermal perception. In this regard, the CPT test appears to be less discriminative in the evaluation of nerve damage than thermal QST. The current result may be supported by the evidence that the Neurometer CPT stimulates nerves directly with an intensity far below what is required to activate the receptor[17,36] and is thus less discriminative on the type of nerve injury (axonal or demyelinating).[37]

To the best of the authors' knowledge, this study is the first to identify and characterize thermal sensory profiles by using cluster analysis in patients with iatrogenic trigeminal nerve injury. A nonhierarchical cluster analysis based on the thermal QST data identified three clusters with distinct thermal sensory profiles. Three subgroups characterized by cluster analysis indicated the severity of damage to the myelinated A-delta and unmyelinated C-fibers; the thermal sensory profile of cluster 1 indicates the most severe damage to both A-delta and C-fibers and indicates the least severe damage in cluster 3. The above results correspond to the fact that thermal QST is appropriate for characterizing axonopathy.[9,38] The large between-side differences in both cold and warm perception, of course, indicate the severe axonal damage. Considering that the sensory recovery is dependent on the degree and the type of nerve injury,[6] it could be easily conjectured that sensory recovery would be late or incomplete in patients with severely decreased thermal perception.

The sum score of objective symptoms was the highest in cluster 3 and the lowest in cluster 1, but self-rating for sensory discomfort was not statistically

different among the clusters. This result indicates that objective symptoms rather than subjective symptoms could identify the degree of nerve damage assessed by thermal QST. Negative symptoms like anesthesia and hypoesthesia were frequent in cluster 1, and this result clearly indicates that the more severe the nerve damage, the more the deficit of sensation. On the other hand, positive symptoms (hyperesthesia and combined type hypoesthesia and hyperesthesia) in clusters 2 and 3 were numerically superior to cluster 1. In accordance with the current study, Gottrup et al demonstrated that loss of thermal sensation to warm and cold stimuli was less in patients with pain than in patients without pain after breast cancer surgery.[27] Taken together, these findings suggest that a relatively small loss of thermal sensation indicates a sensitization of nociceptors. These findings are supported by previous studies on peripheral nerve injury that reported that the less severe the axon damage, the more frequent the neuropathic pain.[12,39]

Methodologic limitations should be mentioned. First, the design of the current study was not longitudinal but cross-sectional, and thus the criteria for stratification of the patients into acute and chronic groups were arbitrary according to the time to the first examination since the injury–that is, the acute group in this study could have probably included patients with temporary and permanent injury. However, the authors believe that comparison of thermal perception according to the time since injury still provides insight into predicting the prognosis. To improve evidence, further research with the criteria of the time until recovery is warranted. Second, the study included symptomatic patients only and this might raise an issue on subject bias. Clinically controlled studies that include a control group without symptoms should be performed. Third, this study used psychophysical modalities, and these measures always have the chance for overestimation of negative or positive symptoms in malingering patients. This bias is attributable to the inherent limitation of QST as a psychophysical test. Thus, psychological assessment as a covariate should be considered in further studies.

Conclusions

Data from this cross-sectional study demonstrated that thermal QST is a sensitive tool for evaluating and characterizing trigeminal nerve injury. Three subgroups with different thermosensory profiles showed that the less damage incurred, the more neuropathic pain experienced. In particular, loss of warm perception might play a pivotal role in the chronicity and severity of subjective sensory symptoms. To further elucidate the mechanistic evidence of neuropathic pain from peripheral nerve injury, longitudinal cohort studies are warranted with a multimodal exploration study design of all cases since their time of injury.

Acknowledgments

The present research was conducted by research funding from Dankook University in 2014. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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