Chairside Intraoral Qualitative Somatosensory Testing: Reliability and Comparison Between Patients with Atypical Odontalgia and Healthy Controls

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Aims: To assess intraoral inter- and intraexaminer reliability of three qualitative measures of intraoral somatosensory function and to compare these measures between patients with atypical odontalgia (AO) and healthy controls. Methods: Thirty-one AO patients and 47 healthy controls participated. Inter- and intraexaminer reliability was tested on a subgroup of 46 subjects (25 AO; 21 healthy). Sensitivity to touch, cold, and pinprick stimuli was evaluated on the painful gingival site and the corresponding contralateral site in AO patients, and bilaterally on the gingiva of the first maxillary premolars in controls. Patients were asked to report hypersensitivity, hyposensitivity, or normal sensitivity to stimuli on the painful site compared with the nonpainful site. Kappa values were calculated, and chi-square and Fisher's exact tests were used to compare frequencies between groups. Results: Kappa values ranged between 0.63 and 0.75. The frequency of hypersensitivity to either modality was significantly higher in patients (29% to 61%) than in controls (9% to 17%) ($\mathbb{P} < .015$), whereas reports of hyposensitivity were similar between groups (2% to 16%) (P > .057). Only 3.2% of the AO patients had no reports of abnormal sensitivity on any of the tests, compared with 59.6% of the healthy subjects (P < .001). **Conclusion:** Intraoral qualitative somatosensory testing can detect intraoral sensory disturbances in AO patients, and the reliability is sufficient for initial screening of orofacial somatosensory function. J OROFAC PAIN 2013;27:165–170. doi: 10.11607/jop.1062

Key words: atypical odontalgia, intraoral, neuropathic pain, reliability, somatosensory testing

In patients with persistent orofacial pain, assessment of somatosensory function is recommended as part of a comprehensive work-up.^{1,2} Recent guidelines from the task force for evaluation of intraoral somatosensory function advocate a standardized battery of quantitative sensory tests (QST).¹ Current guidelines for intraoral QST are derived from the protocol described by the German Research Network on Neuropathic Pain (DFNS).³ This protocol is useful for creation of so-called somatosensory profiles, which may serve to divide patients suffering from the same neuropathic pain condition into subgroups sharing specific features of gain and/or loss of somatosensory function.^{4,5}

However, outside of hospitals and university clinics, access to QST is limited due to the expense of the required equipment, the need for highly trained and calibrated examiners, and the time-consuming nature of the examination. Therefore, although perhaps not as sensitive as the QST, a chairside qualitative somatosensory testing (QualST) of hypersensitivity/hyposensitivity to touch, cold, and pinprick stimulation may be useful in primary care clinical settings because it can be carried out quickly, without expensive equipment.⁶ Such qualitative tests have been used for many years,⁷ despite the fact that, to the authors' knowledge, the reliability of such testing has not been evaluated systematically.

Atypical odontalgia (AO) is an enigmatic chronic intraoral pain condition. It is characterized by pain in a tooth or persistent pain after tooth extraction with no signs of pathology in clinical or radiographic examinations.^{6,8-12} There have been recent proposals to revise the name of the condition, and persistent dentoalveolar pain (PDAP) and peripheral painful trigeminal traumatic neuropathy (PPTNN) have been suggested as more suitable terms.^{13,14} Based on research on the possible underlying pain mechanisms of AO, the currently prevailing hypothesis is that it may be a neuropathic pain condition initiated by the lesion of small primary trigeminal afferent nerve fibers, eg, during oral surgery or endodontic procedures.9 One reason to suspect that AO may be a neuropathic pain condition is the finding that somatosensory abnormalities can be detected in 85% of AO patients.6

The aims of this multicenter study were to assess intraoral inter- and intraexaminer reliability of three qualitative measures of intraoral somatosensory function and to compare these measures between patients with AO and healthy controls. The hypotheses were: (1) inter- and intraexaminer reliability of simple chairside QualST was good and (2) side-to-side differences in response to QualST were more frequently reported in AO patients than in healthy controls.

Materials and Methods

The study received institutional human subject experimentation and local ethics committee approval for all three centers and informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki.

Subjects

Thirty-one AO patients (25 women, 6 men; mean age [\pm SD]: 54 \pm 13 years) and 47 healthy controls (32 women, 15 men; mean age [\pm SD]: 47 \pm 12 years) were recruited from Malmö University (Sweden), University of Washington (USA), and Aarhus University (Denmark). Of these subjects, a total of 46 subjects (34 women, 12 men; mean age [\pm SD]: 53 \pm 14 years; 25 AO patients and 21 healthy subjects) from Malmö and Aarhus participated in the reliability part of the study. All patients were thoroughly examined extra- and intraorally, and

relevant imaging techniques were used (intraoral radiographs were taken for all patients; for some patients, cone beam computed tomography [CBCT] and/or magnetic resonance imaging [MRI] was also used). Most patients had seen several dental and medical specialists in their search for diagnosis and management. Inclusion criteria for AO patients were: > 18 years of age, pain for more than 6 months in a tooth, or persistent pain after tooth extraction with no signs of pathology in clinical or radiographic examinations. 6,8-12 The AO pain must have been present during most of the day and nonparoxysmal.¹⁵ Exclusion criteria for AO patients were: presence of other known orofacial pain conditions, such as odontogenic pain, trigeminal neuralgia, cluster headache, etc. Patients with temporomandibular disorders (TMD) were not excluded, as long as the patient could clearly distinguish between the two pain conditions. The dentists who assessed the patients for the study were all experienced orofacial pain researchers and clinicians. Exclusion criteria for the healthy subjects were: orofacial pain, medical illness, or psychiatric illness.

The AO subjects included in the study were characterized according to present AO pain intensity on a 0-to-10 visual analog scale (VAS), duration of the AO pain in months, Axis I of the Research Diagnostic Criteria for TMD (RDC/TMD), and depression and somatization scores from the Symptoms Checklist (SCL-90) taken from the Axis II questionnaire of the RDC/TMD.¹⁶

QualST

In AO patients, sensitivity to touch, cold, and pinprick stimuli was evaluated on the buccal gingiva adjacent to the painful site and the corresponding contralateral "mirror-image" gingival site. The stimuli were always applied to the nonpainful side first, followed by the painful side. The touch stimulus was applied with a cotton swab in a single stroke over 1 to 2 cm of oral mucosa. The cold stimulus was applied with a stainless steel dental spatula (kept cool in ice water, ~ 0° C) for 1 to 2 seconds. The pinprick stimulus was applied with a dental examination probe with moderate force (a force that was painful but would not penetrate the gingival surface) on the gingiva for ~ 1 second. The cold and pinprick stimuli are often painful in healthy people. No specific attempts to calibrate examiners to a specific force level were made. Patients were asked to report hypersensitivity, hyposensitivity, or normal sensitivity/-algesia to touch, cold, and painful stimuli on the painful site compared with the nonpainful contralateral site. In healthy subjects, the tests were

performed bilaterally on the buccal gingiva adjacent to the canines and first maxillary premolars, right side before left side. The healthy subjects were asked to compare sensitivity between sides. If sides were not perceived to be equally sensitive, they were asked to report any difference (hypersensitivity or hyposensitivity) on the left side by using the right side as the reference.

Reliability

All 46 participants in the reliability evaluation were examined twice by the same examiner on two separate occasions separated by 1 to 2 weeks (intraexaminer reliability). Twenty-eight of these participants were reexamined on the first day by a second blinded examiner (interexaminer reliability).

Statistical Analyses

Cohen's kappa values for the three stimulus modalities were calculated for assessment of intra- and interexaminer reliability. For kappa, values ≤ 0.20 were considered poor agreement; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, good; and 0.81 to 1.00, excellent.¹⁷ Chi-square tests were used to analyze differences in frequency of hypersensitivity, hyposensitivity, or normal sensitivity between groups for the three different stimulus modalities. Similarly, the frequency of $0, \ge 1, \ge 2$, or 3 abnormal (hyper- or hyposensitivity/-algesia) between groups were compared with chi-square tests. Post-hoc analyses between subgroups of AO patients with (n = 9) and without (n = 20) painful TMD were performed using Fisher's exact tests. The sensitivity and specificity of the QualST as diagnostic tests for AO were calculated using the clinical diagnosis (AO or healthy) as the gold standard. Values of P less than .05 were considered statistically significant.

Results

Patient Characteristics

The AO patients had a mean (\pm SD) present pain intensity of 4.6 \pm 2.3 on a 0-to-10 VAS. The average pain duration at the time of inclusion was 99 \pm 60 months (range 18 to 240 months). Twelve AO patients had comorbid TMD diagnoses (three disc-related [group II] diagnosis with no pain, five myofascial TMD [Ia or Ib] in combination with arthralgia [IIIa], and four myofascial TMD alone; ie, a total of nine AO patients with comorbid painful TMD). The mean (\pm SD) depression score of the

Patients and Healthy Controls Combined, $n = 46$)						
	Interexaminer (κ)	Intraexaminer (κ)				
Touch	0.63	0.68				
Cold	0.75	0.75				
Pinprick	0.63	0.70				

Table 1 Overall Test-Retest Reliability (Atypical Odontalgia

SCL-90 was 0.84 ± 0.84 (range 0.00 to 2.95) and the mean score for nonspecific physical symptoms was 0.99 ± 0.74 (range 0.00 to 2.33).

Reliability

Overall, intra- and interexaminer reliability kappa values of intraoral qualitative sensory tests were in the range of 0.63 to 0.75 in the combined dataset including AO patients and controls. This range of values is normally considered to be of good reliability¹⁷ (Table 1). Kappa values were similar between the three stimulus modalities (touch, cold, and pinprick) and were generally higher in healthy subjects than in AO patients (Table 2).

QualST Findings in AO Patients and Healthy Controls

The QualST tests took approximately 2 to 3 minutes per participant. The frequency of hypersensitivity to either modality was significantly higher in AO patients (29% to 61%) than in controls (9% to 17%) (P = .015), whereas reports of hyposensitivity were similar between groups (2% to 16%) (P = .057) (Fig 1). The frequency of subjectively reported normal sensitivity to each stimulus modality (touch, cold, or pinprick) was significantly lower in AO patients (23% to 58%) than in healthy subjects (68% to 91%) (P < .001) (Fig 1).

The frequency of abnormal findings, ie hyper- or hyposensitivity to $0, \ge 1, \ge 2$, or 3 stimulus modalities is shown in Table 3. Only 3.2% of the AO patients had no reports of hyper- or hyposensitivity/-algesia on any of the qualitative tests, compared with 59.6% of the healthy subjects (P < .001) (for further results, see Table 3).

In the subgroup analyses between AO patients with and without painful TMD, it was demonstrated that for touch stimuli, there were no significant differences in the frequency of hypersensitivity, hyposensitivity, or normal sensitivity (P = .862). However, for cold and pinprick stimulation, there were significantly more frequent reports of hypersensitivity on the painful AO side compared with the non-AO side in patients with comorbid

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Table 2	Test-Retest Reliability in Atypical Odontalgia (AO) Patients (n = 25) and Healthy Controls (n = 21)					
	Interexaminer reliability (κ)		Intraexaminer reliability (κ)			
	AO	Healthy	AO	Healthy		
Touch	0.53	1.00	0.60	1.00		
Cold	0.68	0.65	0.61	1.00		
Pinprick	0.53	0.47	0.43	1.00		

Table 3 Number of Abnormal Findings (Hyper- or Hyposensitivity/-algesia) in AO patients (n = 31) and Side-to-Side Differences in Healthy Controls (n = 47)

No. of abnormal findings (%)	AO patients (%)	Healthy controls (%)	Between-group P value
0	3.0	59.6	< .001
≥ 1	96.8	40.4	< .001
≥ 2	58.1	14.9	< .001
3	25.8	2.1	< .001



Fig 1 Pie charts showing the proportions of patients with atypical odontalgia (AO) (n = 31) and healthy controls (n = 47) with intraoral normal sensitivity, hyper, or hyposensitivity/-algesia to touch (gentle stroke with a cotton swab), cold (ice-cold stainless steel spatula), and pinprick (dental explorer). *Indicates statistically significant difference between groups (P < .015). # Indicates a tendency towards significant difference between groups (P = .057).

painful TMD than in AO patients without painful TMD (P < .027).

Sensitivity and Specificity of QualST

To distinguish AO patients from healthy controls, the sensitivity and specificity of different numbers of abnormal QualST results (hypersensitivity or hyposensitivity; range 0 to 3 tests), with the clinical diagnosis as the reference standard, were as follows: no abnormal test: sensitivity 96.8%, specificity 59.6%; \geq 2 abnormal tests: sensitivity 58.1%, specificity 85.1%; 3 abnormal tests: sensitivity 25.8%, specificity 97.9%.

Discussion

The first main finding of this study was that interand intraexaminer reliability of simple intraoral qualitative sensory testing (QualST), which requires only a few minutes, is good but not excellent. The kappa values from the present study are actually quite similar to those previously reported for intraoral QST, which lasts approximately 30 minutes per test site.^{1,18} Thus, in a clinical setting without access to sophisticated QST equipment, this simple battery of tests can be easily applied in a primary care setting as a screening of intraoral (painful and

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nonpainful) somatosensory function with reasonable reliability. With intraoral QST, the authors found intra- and interexaminer reliability of mechanical detection threshold to be in the fair range, where intraoral QualST evaluation of touch sensitivity is good. In contrast, reliability of mechanical pain threshold determination in intraoral QST is better (~ 0.85) than the corresponding QualST measure of pinprick sensitivity. For cold sensitivity, QST and QualST are similar in terms of reliability.

The second main finding of this study was the significant differences between AO patients and healthy controls in intraoral QualST. Especially hypersensitivity and hyperalgesia were more commonly reported in AO patients compared with healthy subjects. In contrast, hyposensitivity was not significantly more frequently reported in AO patients compared with controls, despite a tendency towards it with regard to touch sensitivity (P = .057). The present finding of simple and patient-based qualitative measures of abnormal sensitivity in AO patients is interesting, since studies using QST have mostly shown slight (and what would often seem to be subclinical) changes in somatosensory sensitivity in AO patients compared with healthy controls.^{6,9,12,14,19,20} The low frequency of hyposensitivity to the three stimulus modalities was especially surprising, since neuropathic pain conditions are often characterized by pain in a distinct neuroanatomically plausible region with reduced somatosensory sensitivity.²¹ Yet, in the latest grading system of certainty for the presence of neuropathic pain, the presence of negative or positive neurologic signs concordant with the distribution of pain is considered one of several possible confirmatory tests.^{6,14,21}

Normal sensitivity to all three intraoral stimulus modalities in the present study was actually only reported in 1 out of 31 AO patients (3.2%) in comparison with 59.6% of the healthy subjects. This means that 40.4% of the healthy subjects did not consider sensitivity to all three stimulus modalities to be equal between sides, indicating a high risk of false positives. At the other end of the scale, 25.8% of the AO patients indicated abnormal sensitivity (hyper- or hyposensitivity/-algesia) to all three stimulus modalities in comparison with only 2.1% of the healthy subjects (Table 3). Unfortunately, none of the cutoff points of number of abnormal tests provided acceptable levels of both diagnostic sensitivity and specificity. It could be suggested to add a few more qualitative sensory tests (for example, sensitivity to a warm stimulus, sensitivity to repetitive pinprick,⁶ and occurrence of [cold] allodynia²²) to this QualST battery and test the sensitivity and specificity of the number of abnormal QualST findings (0 to

6) as an easy diagnostic test for AO suitable for use in the primary care setting. This would have to be done using a proper "gold standard," which at present has not been fully established. A gold standard for AO diagnosis could possibly include imaging techniques, electrophysiological techniques, biopsy, QST, pharmacological evaluation, and psychosocial parameters.^{1,9,12,18,20,23-25} Recently, diagnostic criteria for PPTTN were suggested.14 These criteria include a useful estimation of the diagnostic level in line with the grading system for neuropathic pain by Treede et al.²¹ After establishment of a suitable gold standard, another approach with a combination of the QualST with other parameters, such as pain intensity, pain duration, or psychosocial parameters, could also be tested for diagnostic accuracy.

The most important diagnostic challenge in the secondary and tertiary clinical care setting is, however, not to differentiate between AO patients and healthy controls, but rather to distinguish between AO patients and patients with other chronic orofacial pain conditions, eg, of musculoskeletal origin. The present study was not specifically designed or powered to investigate the influence of comorbid conditions such as painful TMD on QualST outcome in AO patients. Nevertheless, an explorative post-hoc analysis was performed, and it indicated that comorbid conditions may indeed be important for the results of the QualST examination, since AO patients with comorbid painful TMD more frequently reported hypersensitivity to cold and pinprick stimuli on the AO pain side than AO patients without painful TMD. The subgroup with comorbid painful TMD was heterogeneous in the sense that it included patients with both myofascial TMD in combination with arthralgia (n = 5) and patients with myofascial TMD alone (n = 4).

Future studies need to address the influence of comorbid pain conditions and associations with generalized hypersensitivity and/or deficiencies in endogenous pain inhibitory control mechanisms on specific orofacial pain conditions. It could be speculated that patients with non-AO chronic and acute orofacial pain conditions (eg, of inflammatory origin—pulpitis, apical periodontitis, etc) may also show a higher frequency of abnormal intraoral QualST than healthy subjects due to involvement of peripheral and central sensitization mechanisms, and this should be investigated in future studies. The authors agree that specialized clinics would benefit from a more sophisticated diagnostic workup that includes QST, imaging techniques, and neurophysiological testing, as has previously been recommended.^{1,2,18,23,26-28}

Conclusions

Reliability of a simple chairside qualitative somatosensory examination was found to be sufficient for an initial screening of orofacial somatosensory function. This quick and simple chairside evaluation of intraoral somatosensory function can detect intraoral sensory disturbances in AO patients, mainly in the form of hypersensitivity.

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References

- Svensson P, Baad-Hansen L, Pigg M, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions—A taskforce report. J Oral Rehabil 2011;38:366–394.
- Svensson P, Baad-Hansen L, Thygesen T, Juhl GI, Jensen TS. Overview on tools and methods to assess neuropathic trigeminal pain. J Orofac Pain 2004;18:332–338.
- Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain 2006;10:77–88.
- Maier C, Baron R, Tolle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150: 439–450.
- Pfau DB, Rolke R, Nickel R, Treede RD, Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and fibromyalgia syndrome. Pain 2009;147:72–83.
- List T, Leijon G, Svensson P. Somatosensory abnormalities in atypical odontalgia: A case-control study. Pain 2008; 139:333–341.
- 7. Hillerup S. Iatrogenic injury to the inferior alveolar nerve: Etiology, signs and symptoms, and observations on recovery. Int J Oral Maxillofac Surg 2008;37:704–709.
- Melis M, Lobo SL, Ceneviz C, et al. Atypical odontalgia: A review of the literature. Headache 2003;43:1060–1074.
- 9. Baad-Hansen L. Atypical odontalgia—Pathophysiology and clinical management. J Oral Rehabil 2008;35:1–11.
- List T, Leijon G, Helkimo M, Oster A, Svensson P. Effect of local anesthesia on atypical odontalgia—A randomized controlled trial. Pain 2006;122:306–314.
- 11. Baad-Hansen L, List T, Jensen TS, Svensson P. Increased pain sensitivity to intraoral capsaicin in patients with atypical odontalgia. J Orofac Pain 2006;20:107–114.

- Baad-Hansen L, List T, Kaube H, Jensen TS, Svensson P. Blink reflexes in patients with atypical odontalgia and matched healthy controls. Exp Brain Res 2006;172: 498–506.
- Nixdorf DR, Drangsholt MT, Ettlin DA, et al. Classifying orofacial pains: A new proposal of taxonomy based on ontology. J Oral Rehabil 2012;39:161–169.
- 14. 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;26:49–58.
- Woda A, Pionchon P. A unified concept of idiopathic orofacial pain: Clinical features. J Orofac Pain 1999;13:172–184.
- Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992; 6:301–355.
- 17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
- Pigg M, Baad-Hansen L, Svensson P, Drangsholt M, List T. Reliability of intraoral quantitative sensory testing (QST). Pain 2010;148:220–226.
- Baad-Hansen L, Leijon G, Svensson P, List T. Comparison of clinical findings and psychosocial factors in patients with atypical odontalgia and temporomandibular disorders. J Orofac Pain 2008;22:7–14.
- Baad-Hansen L, Juhl GI, Jensen TS, Brandsborg B, Svensson P. Differential effect of intravenous S-ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain. Pain 2007;129:46–54.
- Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain. Redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–1635.
- 22. Zagury JG, Eliav E, Heir GM, et al. Prolonged gingival cold allodynia: A novel finding in patients with atypical odontalgia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:312–319.
- Jääskeläinen SK, Teerijoki-Oksa T, Forssell H. Neurophysiologic and quantitative sensory testing in the diagnosis of trigeminal neuropathy and neuropathic pain. Pain 2005;117:349–357.
- Pigg M. Chronic intraoral pain—Assessment of diagnostic methods and prognosis. Swed Dent J Suppl 2011;220:7–91.
- Pigg M, List T, Petersson K, Lindh C, Petersson A. Diagnostic yield of conventional radiographic and cone-beam computed tomographic images in patients with atypical odontalgia. Int Endod J 2011;44:1092–1101.
- Jääskeläinen SK. The utility of clinical neurophysiological and quantitative sensory testing for trigeminal neuropathy. J Orofac Pain 2004;18:355–359.
- Jääskeläinen SK. Clinical neurophysiology and quantitative sensory testing in the investigation of orofacial pain and sensory function. J Orofac Pain 2004;18:85–107.
- Jääskeläinen SK, Forssell H, Tenovuo O. Electrophysiological testing of the trigeminofacial system: Aid in the diagnosis of atypical facial pain. Pain 1999;80:191–200.