Reviewer’s report

Title: Profiling intraoral neuropathic disturbances following lingual nerve injury and in burning mouth syndrome

Version: 1 Date: 31 Oct 2016

Reviewer: Tara Renton

Reviewer's report:

REF OHEA-D-16-00307R1

Title Profiling intraoral neuropathic disturbances following lingual nerve injury and in burning mouth syndrome

Authors Amely Gundula Hartmann, DDS; Robin Seeberger, MD, DDS; Malte Bittner, MD, DDS; Roman Rolke, MD; Claudia Welte-Jzyk; Monika Daubländer, MD, DDS

BMC Oral Health

Justification

Why is there data regarding Inferior alveolar nerve injuries as they were not part of the study?

Methodology

IHS criteria were used for diagnosis of BMS however did the authors intend to explore which of the three sub groups of BMS the patients complied with according to the publicationKolkka-Palomaa M. et al Oral Dis. 2015 Nov;21(8):937-48. doi: 10.1111/odi.12345. Epub 2015 Jun 25. Pathophysiology of primary burning mouth syndrome with special focus on taste dysfunction: a review.

On this basis alone the cohort numbers of; LNI 4 BMS 5 and control 8 are insufficient to make conclusions about sensory thresholds. If you compare with other studies normally using teh thenar as a control non ral site the cohort numbers exceed 20 -40

25% or 2 of the 8 control patients had comorbid headaches which is likely confounding and what comorbidites existed in teh experimental groups?
I am not sure about the stopping the anticagulants for 48 hours would no confound QST results. Most patients on these medications can only come off them incrementally so sudden cessation is not recommended.

QST was undertaken in accordance with the German Research Network taking 90 minute per individual. This is very time consuming and one wonders what the effects are on the sensory thresholds (wind up etc).

Ethical permission There is no mention of ethical reference number for the study.

Results

The warm hypoesthesia and hypoalgesia in the LNI group compared with controls and BMS cold hyperalgesia were similarly reported in a much larger cohort of patients recently.


Conclusions

It is surprising that the foot control site showed no significant differences in BMS patients and perhaps the thenar of the hand as recommended by Rolke et al should be considered as reported by several other studies (see reference list below).

Some statements cannot be supported by the evidence presented.

Overall recommendation

This is a well written and well executed study assessing QST of the lingual mucosa (and foot for BMS control sites) There is no mention of ethical permission. There are some methodological issues including the very small cohorts of LNI, BMS and control subjects and the an oversight in considering three subtypes of BMS patients.

I am concerned overall the paper does not add new information provided by larger previous studies and perhaps the authors should enlarge their cohorts before publication and using the thenar as a control site in all cohorts to clarify central sensitisation in these patients.

There are many repetitions throughout the paper.
Abstract

OBJECTIVE:
The pathophysiology of primary burning mouth syndrome (BMS) has remained enigmatic, but recent studies suggest pathology within the nervous system at multiple levels. This study aimed to investigate in detail the contribution of either focal or generalized alterations within the peripheral nervous system (PNS) in the etiopathogenesis of BMS.

SUBJECTS AND METHODS:
Intraepithelial nerve fiber density (IENFD) of tongue mucosa was assessed in 10 carefully characterized BMS, and the results were compared to 19 age- and gender-matched cadaver controls, 6 with lifetime diabetes. Extensive neurophysiologic and psychophysical examinations of the trigeminal system and distal extremities were performed to profile PNS function in BMS.

RESULTS:
Patients with BMS had significantly fewer intraepithelial nerve fibers (0.27, s.e. 0.18 mm(-1); P = 0.0253) than non-diabetic controls (0.92, s.e. 0.15 mm(-1)). In the subepithelial space, the amount of nerve fibers did not differ between the groups. The majority (9/10) of patients with BMS showed neurophysiologic or psychophysical signs of a more generalized PNS dysfunction.

CONCLUSIONS:
Our results in neurophysiologically optimally characterized BMS patients confirm that pure focal small fiber neuropathy of the oral mucosa has a role in the pathophysiology of primary BMS. Furthermore, BMS may be related to a more generalized, yet subclinical peripheral neuropathy.


Pathophysiology of primary burning mouth syndrome with special focus on taste dysfunction: a review.
Kolkka-Palomaa M1, Jääskeläinen SK2,3, Laine MA4, Teerijoki-Oksa T1, Sandell M5,6, Forssell H4.

Author information

Abstract

Primary burning mouth syndrome (BMS) is a chronic oral condition characterized by burning pain often accompanied with taste dysfunction and xerostomia. The most compelling evidence concerning BMS pathophysiology comes from studies on the somatosensory system using neurophysiologic or psychophysical methods such as blink reflex, thermal quantitative sensory testing, as well as functional brain imaging. They have provided convincing evidence for neuropathic involvement at several levels of the somatosensory system in BMS pain pathophysiology. The number of taste function studies trying to substantiate the subjective taste disturbances or studies on salivary factors in BMS is much more limited, and most of them suffer from definitional and methodological problems. This review aims to critically evaluate the existing literature on the pathophysiology of BMS, paying special attention to the correctness of case selection and the methodology used in published studies, and to summarize the current state of knowledge. Based on the recognition of several gaps in the current understanding of the pathophysiology of BMS especially as regards taste and pain system interactions, the review ends with future scenarios for research in this area.


Thermal and mechanical quantitative sensory testing in Chinese patients with burning mouth syndrome--a probable neuropathic pain condition?

Author information
Abstract

BACKGROUND:

To explore the hypothesis that burning mouth syndrome (BMS) probably is a neuropathic pain condition, thermal and mechanical sensory and pain thresholds were tested and compared with age- and gender-matched control participants using a standardized battery of psychophysical techniques.

METHODS:

Twenty-five BMS patients (men: 8, women: 17, age: 49.5 ± 11.4 years) and 19 age- and gender-matched healthy control participants were included. The cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT) and mechanical pain threshold (MPT), in accordance with the German Network of Neuropathic Pain guidelines, were measured at the following four sites: the dorsum of the left hand (hand), the skin at the mental foramen (chin), on the tip of the tongue (tongue), and the mucosa of the lower lip (lip). Statistical analysis was performed using ANOVA with repeated measures to compare the means within and between groups. Furthermore, Z-score profiles were generated, and exploratory correlation analyses between QST and clinical variables were performed. Two-tailed tests with a significance level of 5% were used throughout.

RESULTS:

CDTs (P < 0.02) were significantly lower (less sensitivity) and HPTs (P < 0.001) were significantly higher (less sensitivity) at the tongue and lip in BMS patients compared to control participants. WDT (P = 0.007) was also significantly higher at the tongue in BMS patients compared to control subjects. There were no significant differences in MDT and MPT between the BMS patients and healthy subjects at any of the four test sites. Z-scores showed that significant loss of function can be identified for CDT (Z-scores = -0.9 ± 1.1) and HPT (Z-scores = 1.5 ± 0.4). There were no significant correlations between QST and clinical variables (pain intensity, duration, depressions scores).

CONCLUSION:

BMS patients had a significant loss of thermal function but not mechanical function, supporting the hypothesis that BMS may be a probable neuropathic pain condition. Further studies including e.g. electrophysiological or imaging techniques are needed to clarify the underlying mechanisms of BMS.
Quantitative methods for somatosensory evaluation in atypical odontalgia.

Porporatti AL1, Costa YM1, Stuginski-Barbosa J1, Bonjardim LR2, Conti PC1, Svensson P3.

Author information

Abstract

A systematic review was conducted to identify reliable somatosensory evaluation methods for atypical odontalgia (AO) patients. The computerized search included the main databases (MEDLINE, EMBASE, and Cochrane Library). The studies included used the following quantitative sensory testing (QST) methods: mechanical detection threshold (MDT), mechanical pain threshold (MPT) (pinprick), pressure pain threshold (PPT), dynamic mechanical allodynia with a cotton swab (DMA1) or a brush (DMA2), warm detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT), cold pain detection (CPT), and/or wind-up ratio (WUR). The publications meeting the inclusion criteria revealed that only mechanical allodynia tests (DMA1, DMA2, and WUR) were significantly higher and pain threshold tests to heat stimulation (HPT) were significantly lower in the affected side, compared with the contralateral side, in AO patients; however, for MDT, MPT, PPT, CDT, and WDT, the results were not significant. These data support the presence of central sensitization features, such as allodynia and temporal summation. In contrast, considerable inconsistencies between studies were found when AO patients were compared with healthy subjects. In clinical settings, the most reliable evaluation method for AO in patients with persistent idiopathic facial pain would be intraindividual assessments using HPT or mechanical allodynia tests.


Intraoral somatosensory abnormalities in patients with atypical odontalgia--a controlled multicenter quantitative sensory testing study.

Baad-Hansen L1, Pigg M, Ivanovic SE, Faris H, List T, Drangsholt M, Svensson P.

Author information

Abstract

Intraoral somatosensory sensitivity in patients with atypical odontalgia (AO) has not been investigated systematically according to the most recent guidelines. The aims of this study were
to examine intraoral somatosensory disturbances in AO patients using healthy subjects as reference, and to evaluate the percent agreement between intraoral quantitative sensory testing (QST) and qualitative sensory testing (QualST). Forty-seven AO patients and 69 healthy control subjects were included at Universities of Washington, Malmö, and Aarhus. In AO patients, intraoral somatosensory testing was performed on the painful site, the corresponding contralateral site, and at thenar. In healthy subjects, intraoral somatosensory testing was performed bilaterally on the upper premolar gingiva and at thenar. Thirteen QST and 3 QualST parameters were evaluated at each site, z-scores were computed for AO patients based on the healthy reference material, and LossGain scores were created. Compared with control subjects, 87.3% of AO patients had QST abnormalities. The most frequent somatosensory abnormalities in AO patients were somatosensory gain with regard to painful mechanical and cold stimuli and somatosensory loss with regard to cold detection and mechanical detection. The most frequent LossGain code was L0G2 (no somatosensory loss with gain of mechanical somatosensory function) (31.9% of AO patients). Percent agreement between corresponding QST and QualST measures of thermal and mechanical sensitivity ranged between 55.6% and 70.4% in AO patients and between 71.1% and 92.1% in control subjects. In conclusion, intraoral somatosensory abnormalities were commonly detected in AO patients, and agreement between quantitative and qualitative sensory testing was good to excellent.


Somatosensory abnormalities in atypical odontalgia: A case-control study.

List T1, Leijon G, Svensson P.

Author information

Abstract

Somatosensory function in patients with persistent idiopathic types of orofacial pain like atypical odontalgia (AO) is not well described. This study tested the hypothesis that AO patients have significantly more somatosensory abnormalities than age- and sex-matched controls. Forty-six AO patients and 35 controls participated. Inclusion criteria for AO were pain in a region where a tooth had been endodontically or surgically treated, persistent pain >6 months, and lack of clinical and radiological findings. The examination included qualitative tests and a battery of intraoral quantitative sensory testing (QST). Most AO patients (85%) had qualitative somatosensory abnormality compared with few controls (14%). The most common qualitative abnormalities in AO patients were found with pin-prick 67.4%, cold 47.8%, and touch 46.5% compared with 11.4%, 8.6%, and 2.9%, respectively, in the control group (P<0.001). Between-group differences were seen for many intraoral QST: mechanical detection threshold, mechanical pain threshold (pinprick), dynamic mechanical alldynia (brush), dynamic mechanical alldynia (vibration), wind-up ratio, and pressure pain threshold (P<0.01). In the trigeminal area, between-group differences in thermal thresholds were nonsignificant while differences in cold detection at
the thenar eminence were significant. Individual somatosensory profiles revealed complex patterns with hyper- and hyposensitivity to intraoral QST. Between-group differences in pressure pain thresholds (P<0.02) were observed at the thenar eminence. In conclusion, significant abnormalities in intraoral somatosensory function were observed in AO, which may reflect peripheral and central sensitization of trigeminal pathways. More generalized sensitization of the nociceptive system may also be part of AO pathophysiology.


Tactile sensory and pain thresholds in the face and tongue of subjects asymptomatic for oro-facial pain and headache.

Okayasu I1, Komiyama O, Ayuse T, De Laat A.

Author information

Abstract

The aim of this study was to examine the tactile sensory and pain thresholds in the face, tongue, hand and finger of subjects asymptomatic for pain. Sixteen healthy volunteers (eight men and eight women, mean age 35±7 years, range 27-41) participated. Using Semmes-Weinstein monofilaments, the tactile detection threshold (TDT) and the filament-prick pain detection threshold (FPT) were measured at five sites: on the cheek skin (CS), tongue tip (TT), palm side of the thenar skin (TS), dorsum of the hand (DH) and the finger tip (FT). The difference between the tactile sensory and pain threshold (FPT-TDT) was also calculated. Both for the TDT and FPT, TT and DH had the lowest and highest values, respectively. As for the FPT-TDT, there were no significant differences among the measurement sites. As the difference between FPT and TDT (FPT-TDT) is known to be an important consideration in interpreting QST (quantitative sensory testing) data and can be altered by neuropathology, taking the FPT-TDT as a new parameter in addition to the TDT and FPT separately would be useful for case-control studies on oro-facial pain patients with trigeminal neuralgia, atypical facial pain/atypical odontalgia and burning mouth syndrome/glossodynia.


Effect of topical lidocaine in the oral and facial regions on tactile sensory and pain thresholds.

Okayasu I1, Komiyama O2, Ayuse T3, De Laat A4.

Author information

Abstract
OBJECTIVE:
The aim of the present study was to examine the effect of lidocaine application to the face, tongue and hand on sensory and pain thresholds of symptom-free subjects.

DESIGN:
Eighteen females (mean age 25.7 years, range 22-38) participated. Using Semmes-Weinstein monofilaments, the tactile detection threshold (TDT) and the filament-prick pain detection threshold (FPT) were measured on the cheek skin (CS), tongue tip (TT) and palm side of the thenar skin (TS). Subjects were tested in 2 sessions at a 1 week interval in randomised order. Lidocaine (session A) or placebo gel (session B) was applied for 5 min. The TDT and FPT were measured before and after application.

RESULTS:
The TDT at all sites in session A significantly increased after 5 min, but a significant session effect on the TDT was only found at the TT (P<0.01). On the other hand, there were significant session effects on the FPT at all sites (P<0.01).

CONCLUSION:
These results indicate that the pain threshold (FPT) is more susceptible to local anesthetics than the sensory threshold (TDT), but further study is needed to use topical lidocaine for the control of oral and facial pain in the clinic.

Pain threshold and pain recovery after experimental stimulation in patients with burning mouth syndrome.
Ito M1, Kurita K, Ito T, Arao M.
Author information
Abstract
The aim of the present study was to examine pain threshold and pain recovery in patients with burning mouth syndrome (BMS) and matched no-pain controls. Twenty female patients diagnosed with BMS without organic gross changes were enrolled in the study. Twenty control
subjects were chosen from age-matched healthy female volunteers. We compared the thermal pain threshold using heat beam dolorimeter on the finger and tongue between patients and controls. Warm (at 50 degrees C for 5 s), cold (at 0 degrees C for 30 s) and mechanical (stimulation by electric tooth brush for 15 s) stimulation was applied to the tongue for both groups. Participants were asked to rate the subjective pain using a visual analogue scale (VAS). Although there was no significant differences between patients and controls in terms of the threshold on the finger, the threshold on the tongue was significantly higher in patients than in controls. We suggest there were peripheral dysfunction at the tongue, and/or central dysfunction in patients with BMS. Among the three types of stimulation, the patients perceived significantly the highest pain from the mechanical stimulation for the first 5 min after the stimulation. Furthermore, when patients with BMS perceived some pain, they continued to complain of the pain longer and more intricately than the controls. This indicates that the pain of the patients is strongly affected not only at a sensory component but also at an affective/motivational component than the controls. However, we should be cautious of simply advancing psychogenic theory in this etiology.


Yilmaz Z, Egbuniwe O, Renton T.

Abstract

AIMS:

To assess thermal pain perception in patients with burning mouth syndrome (BMS) and lingual nerve injury (LNI) by using a quantitative sensory testing (QST) protocol.

METHODS:

QST was used to assess cool, warm, cold pain, and heat pain thresholds in healthy control subjects (n = 17) and in patients with BMS (n = 22) and LNI (n = 47). Capsaicin (10 μg/mL) and ethyl chloride-evoked hypersensitivities at the anterior two-thirds of the tongue were measured using a visual analog scale. Data were analyzed using Microsoft Excel with descriptive statistics, scatter graphs, and two-tailed Student t tests with 95% confidence interval and 5% level of significance.
RESULTS:

Patients with BMS significantly reported the most pain at rest (P < .001) and capsaicin hypersensitivity (P < .01). Despite this increased sensitivity to capsaicin and significantly lower warm threshold than the control subjects (P < .05), these patients did not show heat pain hyperalgesia. There was increased sensitivity to ethyl chloride and cold pain hyperalgesia in patients with BMS (P < .05) compared with reduced or no sensation of cold or heat pain in patients with LNI.

CONCLUSIONS:

This study has demonstrated that the assessment of capsaicin and ethyl chloride-evoked sensitivities as well as the use of QST to assess thermosensitivity are useful approaches for detecting hyperalgesia or hypoalgesia to heat and cold in patients with BMS and LNI.

Co-occurrence of Pain Symptoms and Somatosensory Sensitivity in Burning Mouth Syndrome: A Systematic Review.

Moisset X1,2, Calbacho V3, Torres P3, Gremeau-Richard C1,4, Dallel R1,4.

Author information

Abstract

BACKGROUND:

Burning mouth syndrome (BMS) is a chronic and spontaneous oral pain with burning quality in the tongue or other oral mucosa without any identifiable oral lesion or laboratory finding. Pathogenesis and etiology of BMS are still unknown. However, BMS has been associated with other chronic pain syndromes including other idiopathic orofacial pain, the dynias group and the family of central sensitivity syndromes. This would imply that BMS shares common mechanisms with other cephalic and/or extracephalic chronic pains. The primary aim of this systematic review was to determine whether BMS is actually associated with other pain syndromes, and to analyze cephalic and extracephalic somatosensory sensitivity in these patients.

METHODS:
This report followed the PRISMA Statement. An electronic search was performed until January 2015 in PubMed, Cochrane library, Wiley and ScienceDirect. Searched terms included "burning mouth syndrome OR stomatodynia OR glossodynia OR burning tongue OR oralburning". Studies were selected according to predefined inclusion criteria (report of an association between BMS and other pain(s) symptoms or of cutaneous cephalic and/or extracephalic quantitative sensory testing in BMS patients), and a descriptive analysis conducted.

RESULTS:

The search retrieved 1512 reports. Out of these, twelve articles met criteria for co-occurring pain symptoms and nine studies for quantitative sensory testing (QST) in BMS patients. The analysis reveals that in BMS patients co-occurring pain symptoms are rare, assessed by only 0.8% (12 of 1512) of the retrieved studies. BMS was associated with headaches, TMD, atypical facial pain, trigeminal neuralgia, post-herpetic facial pain, back pain, fibromyalgia, joint pain, abdominal pain, rectal pain or vulvodynia. However, the prevalence of pain symptoms in BMS patients is not different from that in the age-matched general population. QST studies reveal no or inconsistent evidence of abnormal cutaneous cephalic and extracephalic somatosensory sensitivity.

CONCLUSIONS:

There is no evidence for a high rate of other pain symptoms or somatosensory impairments co-occurring with BMS. These results thus suggest that BMS rather depends on specific mechanisms, likely at the trigeminal level. Nevertheless, more thoroughly conducted research is required to draw definitive conclusion.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

No competing interest

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal