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Original Article

Age differences in pain sensitivity and effect of topical lidocaine on the tongue in healthy female subjects

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Abstract

Purpose: To assess the sensitivity and the effect of topical lidocaine on the tongue by quantitative sensory testing, comparing healthy middle-aged female subjects with healthy young female subjects.
Methods: Sixteen healthy female subjects including eight in their fifties and eight in their twenties participated. They participated in two sessions at a 2-week interval in randomized order: lidocaine (experimental session) or placebo gel (placebo session) was applied on the tongue tip for 5min. The following parameters were taken on the tongue tip before and after application of the gel in each session: tactile detection threshold (TDT), filament-prick pain detection threshold (FPT), and numerical rating scale (NRS).
Results: An increase of both TDT and FPT and a decrease of NRS were found after lidocaine application in both middle-aged and young female subjects. In the elder females, an increase of TDT, FPT, and NRS was also found after placebo gel application. However, the changes were not statistically significant, except for FPT in middle-aged subjects.
Conclusion: The reactions found after lidocaine application in middle-aged female subjects could be due to habituation as well as to the post-application effect of placebo gel. Placebo-induced changes appeared more pronounced in the elder females.

Keywords: burning mouth syndrome, lidocaine, neuropathic, nociplastic pain, quantitative sensory testing

Introduction

Burning mouth syndrome (BMS) which is also called stomatodynia and glossodynia (if the symptoms are confined to the tongue only) remains an unclear and poorly understood condition [De Laat A. Pain associated with temporomandibular disorders and with burning mouth syndrome: 147-152, Pain 2010-An Update Review, 2010]. It is characterized by a spontaneous burning sensation in the oral cavity. BMS is classified into primary and secondary. The former has no identifiable local or systemic cause, while the latter is associated with pathology such as mucosal disease, vitamin deficiency, diabetes, or medication side effects. Since the introduction of the international classification for orofacial pain (ICOP) [1], the diagnosis of BMS is only given after ruling out all potential causes (formerly called the primary form). The formerly called “secondary form” is termed “oral burning”.

The etiology of BMS is still unclear. Psychosocial factors and personality profiles have also been proposed as an underlying cause of BMS [2]. There is also some evidence that BMS could be considered a neuropathic pain condition [3], as pioneering and earlier studies have demonstrated somatosensory alteration and dysfunction [4,5]. There are several theories and hypotheses, for example, damaged A-delta fibers, injury of the gustatory A-delta fibers and loss of small-fibers, indicating a trigeminal small-fiber neuropathy [6].

If BMS is considered as a neuropathic pain condition, quantitative sensory testing (QST) could be an important tool in the diagnostic process [7-9]. QST is a standardized method that quantifies sensory alterations to detect changes in fiber and receptor function [10]. It is essential in the diagnosis of trigeminal neuropathic pain, such as trigeminal neuralgia (TN) and post-traumatic neuralgia. It has also been used to assess and quantify somatosensory function in patients with other orofacial pain conditions such as temporomandibular disorder (TMD) and migraine [11-14], but not in the BMS diagnostics so far.

Since its etiology is unclear, not only the diagnosis but also management of BMS is still not established [15]. Based on published randomized clinical trials, topical (clonazepam, lidocaine, capsaicin), systemic (alpha-lipoic acid, selective serotonin reuptake inhibitors, amisulpride) and behavioral therapies have been evaluated. Topical clonazepam (benzodiazepines) is the first-line medication for treatment of BMS [15-17], but generally, it is difficult for dentists to prescribe benzodiazepines. On the other hand, topical lidocaine is familiar to dentists, but has not been evaluated for BMS patients yet. Considering medications for neuropathic pain, topical lidocaine might be useful, as well as topical clonazepam and capsaicin.

If BMS is approached as a neuropathic pain condition, QST and lidocaine could be used for diagnosis and management, respectively. Therefore, this study aimed to assess the effects of topical lidocaine in patients with BMS and/or glossodynia by using QST, in comparison to healthy subjects. BMS-patients are predominantly peri- and postmenopausal women. Before collecting data on patients with BMS and glossodynia, this pilot study was set up to assess the sensitivity and the effect of topical lidocaine on the tongue comparing healthy middle-aged female subjects with healthy young female subjects.

Materials and Methods

Study protocol

Subjects were sixteen healthy female subjects including eight in their fifties and eight in their twenties. Participants were selected from the Nagasaki University Hospital staff and students at Nagasaki University, respectively. Informed consent was obtained from all subjects before the experiment. Subjects were excluded if they were allergic to lidocaine. The institutional ethics committee of Nagasaki University Graduate School of Biomedical Sciences approved this study (No. 1502-4) which was conducted in accordance with the Helsinki Declaration. To avoid inter-individual variability in procedures, one examiner (M.T) performed all measurements.

Each subject undertook two sessions (experimental and placebo sessions) at a 2-week interval in randomized order. A 2% lidocaine gel (AstraZeneca, Osaka, Japan) was applied for 5 min at the tongue tip (experimental session). A placebo gel (Weltec, Osaka, Japan), similar in appearance to the lidocaine, was administered in an identical manner (placebo session). The area covered by lidocaine/placebo gel at the tongue tip was a circle 1cm across, and the amount of gel was approximately 0.2 g. QST was performed before and after application of a lidocaine/placebo gel [18]. The subjects were instructed to protrude their tongue and keep the tongue tip outside the mouth throughout the experiment to avoid the

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possibility that lidocaine/placebo gels were washed out by saliva.

QST

Tactile detection threshold (TDT) and filament-prick pain detection threshold (FPT) were determined using Semmes-Weinstein monofilaments with 20 different diameters (Premier product management, Kent, WA, USA). The number of the filaments (1.65-6.65) corresponds to a logarithmic function of the equivalent forces of 0.0045-447 g. The subjects were instructed to close their eyes during the TDT procedure. The TDT was measured using the stair-case method. The procedure has been already described in detail in previous studies [18-21]. After the TDT measurements, the FPT was examined in the same manner. However, the subjects were instructed to keep their eyes open throughout the FPT procedure. The interval between FPT measurements at the same site was set at 3 min in order to avoid sensitization. Pain intensity of the FPT was also assessed by the numerical rating scale (NRS) ranging from 0 (no pain) to 10 (most pain imaginable). Before the experiment, the Japanese version of the general health questionnaire-60 (GHQ-60) was scored as an evaluation for psychological factors. It was classified into four subscales: (A) somatic symptoms; (B) anxiety/insomnia; (C) social dysfunction; (D) severe depression [7]. Before lidocaine/placebo application, QST was also measured on the palm of the hand (PH) as well as the tongue tip (TT) [7,22].

Z score

For each session, the TDT and FPT were transformed into z scores according to the following expression: z score = (value single – mean group baseline) / SD group baseline. A positive z score (>1.96) denotes a gain of somatosensory function for the tested stimulus, whereas a negative z score (<1.96) indicates a loss of somatosensory function [8,23,24].

Statistical analysis

The unpaired *t*-test (parametric methods) was used for normal distribution of two sample analysis. The QST data were not normally distributed, log transformed before analyses and the differences between healthy middle-aged and young female subjects were analyzed using the un-paired test. The paired test was performed to test effects of the condition (pre- and post-application of lidocaine gel/placebo gel) and the session (post-application of lidocaine gel and placebo gel). Excel-Toukei (for Windows; Bell Curve for Excel) was used for these analyses, and a P value of <0.05 was considered to indicate statistical significance.

Results

Descriptive data of the subjects' characteristics are shown in Table 1. The average age was 56.1 ± 3.0 years (range, 52-59 years) for middle-aged female subjects and 25.5 ± 0.9 years (ranges, 24-27 years) for young female subjects. No significant differences in the height (P = 0.737) and weight (P = 0.858) were observed between middle aged female subjects and young female subjects.

GHQ-60 scores and the four subscales except (C) social dysfunction for young subjects were slightly higher than for middle aged subjects, but there were no significant differences between the two groups (total: P = 0.740, A: P = 0.753, B: P = 0.357, C: P = 0.831, D: P = 0.098) (Table 1).

The TDT, FPT, and NRS on the PH were measured once at the start of the sessions. On the other hand, the TDT, FPT, and NRS on the TT were measured twice before application of lidocaine or placebo both under the same conditions. The two scores of the TDT, FPT, and NRS on the TT before application of lidocaine/placebo gel were averaged in order to obtain a single value (Table 2), because there were no significant differences between these two data for middle-aged subjects (P = 0.059 for TDT, P = 0.161 for FPT, P = 0.581 for NRS) and for young subjects (P = 0.317 for TDT, P = 0.735 for FPT, P = 0.194 for NRS).

Comparing the data between the TT and PH, the TDT and FPT were lower, but the NRS was higher on the TT than those on the PH in both groups (Table 2). A significant difference was found in the TDT (P < 0.0001) for middle-aged subjects.

Although there were no significant differences between two groups, the FPT data both on the TT and PH were lower for young subjects, and their corresponding NRS values were higher for middle aged subjects (Table 2).

The TDT in the experimental session increased from 2.00 (95% CI, 1.843-2.160) to 2.25 (95% CI, 1.666-2.845) for middle-aged subjects and from 1.98 (95% CI, 1.847-2.127) to 2.10 (95% CI, 1.836-2.387) for young subjects (Fig. 1a). In the placebo session, the TDT increased from 1.93 (95% CI, 1.930-1.930) to 2.11 (95% CI, 1.700-2.489) for middle-aged subjects but remained at the same value of 1.99 (95% CI, 1.835-2.157; 1.839-2.158) for young subjects (Fig. 1a). There were no significant differences between pre- and post-application of lidocaine gel/placebo gel for the two groups (Fig. 1a).

The FPT in the experimental session increased from 5.59 (95% CI, 5.145-5.756) to 6.08 (95% CI, 5.702-6.303) for middle aged subjects and from 5.49 (95% CI, 4.919-6.121) to 5.60 (95% CI, 4.897-6.263) for young subjects (Fig. 1b). In the placebo session, the FPT increased from 5.79 (95% CI, 5.450-6.044) to 6.03 (95% CI, 5.567-6.353) for middle aged subjects but remained stable for young subjects (pre: 5.50 [95% CI, 4.904-6.065]; post: 5.49 [95% CI, 4.852-6.008]) (Fig. 1b). Significant differences were found between pre- and post-application of lidocaine gel (P < 0.001) and placebo gel (P = 0.029) for middle-aged subjects (Fig. 1b).

The NRS in the experimental session decreased from 3.38 (95% CI, 1.382-5.332) to 2.94 (95% CI, 0.996-5.147) for middle-aged subjects and from 2.38 (95% CI, 1.075-4.068) to 1.81 (95% CI, 0.783-3.075) for young subjects (Fig. 1c). In the placebo session, the NRS increased from 3.50 (95% CI, 1.253-5.605) to 3.75 (95% CI, 1.073-6.356) for middle-aged subjects but remained stable for young subjects (pre: 1.88 [95% CI, 1.075-2.925]; post: 1.88 [95% CI, 1.245-2.755]) (Fig. 1c). There were no significant differences between pre- and post- application of lidocaine gel/placebo gel for the two groups (Fig. 1c).

Table 3 shows the average z scores after application of lidocaine and placebo gel for middle-aged female subjects and young female subjects. All data were within the range between −1.96 and 1.96, indicating no gain and no loss of somatosensory function regarding the TDT and FPT.

Table 1 Comparison of age, height, weight and psychological test scores between healthy middle-aged female (Middle) and young female (Young) subjects

Subject	Middle	Young	P value
Number	8	8	
Age (years)	56.1 ± 3.0	25.5 ± 0.9	0.014
Height (cm)	158.3 ± 6.8	158.0 ± 4.9	0.737
Weight (kg)	52.1 ± 7.8	50.5 ± 6.9	0.858
GHQ-60			
Total	10.1 ± 7.8	12.4 ± 8.8	0.740
(A)	1.6 ± 1.6	2.5 ± 1.8	0.753
(B)	2.0 ± 1.5	2.8 ± 2.2	0.357
(C)	0.8 ± 1.0	0.5 ± 0.8	0.831
(D)	0.1 ± 0.4	0.5 ± 0.8	0.098

GHQ-60, the general health questionnaire-60. (A) = somatic symptoms; (B) = anxiety/insomnia; (C) = social dysfunction; (D) = severe depression

Table 2 Comparison of quantitative sensory testing (QST) results between healthy middle-aged female (Middle) and young female (Young) subjects

	Middle	Young	P value
TDT			
TT	1.96 ± 0.11	1.98 ± 0.15	0.362
PH	2.29 ± 0.34	2.04 ± 0.21	0.237
FPT			
TT	5.69 ± 0.42	5.49 ± 0.58	0.073
PH	6.30 ± 0.32	5.66 ± 0.64	0.078
NRS			
TT	3.44 ± 2.02	2.13 ± 1.31	0.098
PH	3.06 ± 2.27	2.00 ± 1.28	0.180

TDT, tactile detection threshold; FPT, filament-prick pain detection threshold; NRS, numerical rating scale; TT, tongue tip; PH, palm of the hand

Discussion

A recent QST study suggests that BMS has a neuropathic component in which the mechanical detection threshold showed loss of sensation [8], while other QST studies suggest that BMS may be more related to psychological factors [7]. Topical applications of clonazepam were effective in decreasing pain [25]. However, it is unclear whether lidocaine and/or capsaicin are effective for patients with BMS. When the lingual nerve was

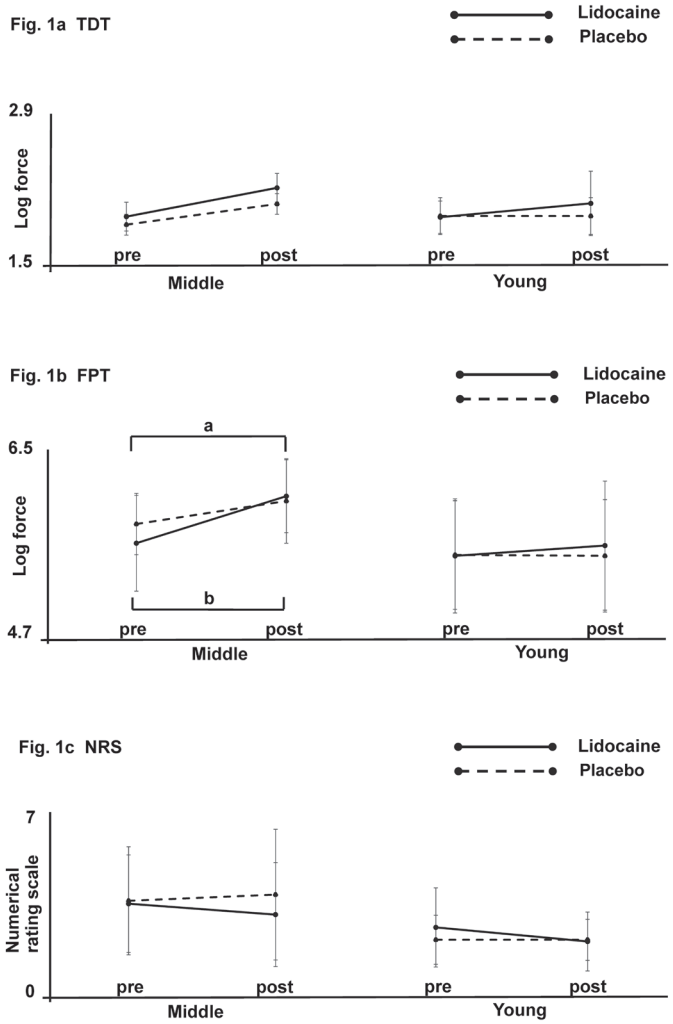

Fig. 1 Tactile detection threshold (TDT) (a), filament-prick pain detection threshold (FPT) (b) and pain rating using numerical rating scale (NRS) (c) calculated before (pre) and after (post) application of lidocaine and placebo gel on the tongue tip for 5 min in healthy middle-aged female (Middle) and young female (Young) subjects. a and b indicate significant differences between pre- and post-application of lidocaine gel and placebo gel, respectively ($P < 0.05$).

Table 3 Individual z scores after application of lidocaine and placebo gel with the use of means and standard deviation of preapplication data as the reference in healthy middle-aged female (Middle) and young female (Young) subjects

	Middle		Young	
	Lidocaine	Placebo	Lidocaine	Placebo
TDT	1.55 ± 3.69	0.00 ± 0.00	0.87 ± 1.98	0.00 ± 1.01
FPT	0.99 ± 0.76	0.75 ± 1.38	0.18 ± 1.12	−0.02 ± 1.03

TDT, tactile detection threshold; FPT, filament-prick pain detection threshold

anesthetized in BMS patients, some of them were completely pain-free, while others did not experience any therapeutic effect [26]. Honda et al. assessed the effect of topical application of capsaicin to the tongue in healthy young women on somatosensory sensitivity using QST [24]. In a previous study, Okayasu et al. examined the effect of lidocaine application to the tongue of symptom-free young women using QST [18]. Since BMS patients are predominantly peri- and postmenopausal women, the results of the two QST studies mentioned above cannot be translated to the BMS, since both targeted only young healthy females. The present study therefore was set up to further investigate the effect of lidocaine on the sensory and pain thresholds of the tongue in elderly female patients with BMS.

In a large percentage of BMS patients psychogenic factors are involved and psychological assessment is needed. Komiyama et al. reported that pain intensity was less severe in BMS than in TN, but the psychosocial impact of BMS was worse than that of TN [27]. That study used the Research Diagnostic Criteria for Temporomandibular Disorders (RDC-TMD) Axis 2 questionnaire [27]. Honda et al. also used the RDC-TMD Axis 2 questionnaire and compared pain intensities and psychosocial characteristics between TMD and BMS patients, which demonstrated that BMS patients had significantly lower pain intensity than TMD patients, but BMS patients especially in the middle-aged group had significantly higher depression scores than TMD patients [28]. Recently, Honda et al. used the GHQ and its scores were significantly higher in BMS patients than in healthy participants [7]. In the present study, there were no significant differences in height, weight and GHQ scores between the two groups, and both physical and psychological conditions were well matched.

Before lidocaine/placebo application, the thresholds themselves (TDT, FPT, and NRS) on the PH were also measured and compared with those on the TT. The results indicated that the TDT and FPT were lower, but the NRS was higher on the TT than those on the PH in accordance with previous studies, which means that the tongue is more sensitive than the skin of the hand [18,20]. It was suggested that this difference could be due to different characteristics of the mechanoreceptors at the tongue and the hand [18,20]: the former are the fast-adapting, and the latter are the slow-adapting mechanoreceptors [Trulsson M et al. Mechanosensation: 165-198, Clinical Oral Physiology, 2004]. In addition, the presence or absence of visual perception might have something to do with this result: compensation for lack of visual perception on the tongue would work but not on the hand [18,20].

The relationship of the FPT and its NRS between the two groups (the FPT data both on the TT and PH were lower for young subjects, and their corresponding NRS values were higher for middle-aged subjects) was similar to a previous study evaluating gender (men vs women) and ethnic (Japanese vs Belgian) differences of the FPT and NRS in the orofacial region of symptom-free subjects [29]: women were more sensitive (a lower value of the FPT) compared with men, and Japanese subjects also were more sensitive compared with the Belgian subjects. However, regarding the NRS, men had a higher value compared with women, and the Belgians had a higher value compared with Japanese [29]. Kim et al. evaluated genetic influences on variability in human pain sensitivity associated with gender, ethnicity, and temperament [30]. In this study, pain sensitivity was more intense for young subjects, but pain expression was bigger for middle-aged subjects. The older the female becomes, the greater she expresses her pain. The age-dependent changes in the FPT and NRS could be explained by experiences in life. Kitagawa et al. found abnormal pain responses in aged rats and suggested a change in mechanisms of nociception with advancing age [31]. Their basic study could be helpful for considering the effects of aging on pain.

A significant increase after post application of lidocaine was found in the FPT for middle-aged subjects. But a significant increase was also found in the placebo session, and there was no significant session effect. This result did not support the effect of lidocaine on the pain threshold and might be explained by habituation. Habituation is a decrease or loss of response following repetitive stimulation [McNeill C et al. What is pain and how do we classify orofacial pain?: 3-11, Orofacial Pain, 2008]. In an imaging study, Shiozaki et al. noted pain habituation to repetitive noxious heat stimuli in healthy controls but not in BMS patients [32]. This also needs to be investigated in BMS patients by QST in future studies with a large sample size.

For middle-aged subjects, a significant increase of the FPT was found but a significant difference was not found in the NRS. Normally, the visual analog scale (VAS) would decrease as the pain threshold increases [33]. But the present study found an increase of both FPT and NRS for middle-aged subjects in the placebo session. Considering it was not found for the younger subjects, age-related changes might occur and cause the distortion of perception and cognition. Therefore, the sensory and pain thresholds measurements (TDT and FPT) and the pain scale assessments (NRS) might reflect perception and cognition conditions, respectively. In particular, the state of cognition might change more easily by aging.

Honda et al. analyzed z scores in a surrogate model of BMS applying topical capsaicin to the tongue in 16 healthy women, and showed somatosensory loss related to cold detection threshold [24]. Watanabe et al. showed loss of sensation against innocuous mechanical stimuli in chronic BMS patients by analyzing mechanical detection threshold (MDT) z scores and suggested that MDT at the tongue could differentiate BMS patients and healthy volunteers [8]. Although z scores in the present study were within the normal range (between −1.96 and 1.96) and showed no

gain and no loss of somatosensory function regarding the TDT and FPT, the z score analysis could be considered and applied in studies on BMS.

For the patients with neuropathic pain conditions, studies have been carried out that reported in topical application of the local anesthetic, lidocaine is effective [34,35]. Kanai et al. and Niki et al. examined the effect of lidocaine delivered via pump spray on pain in patients with post-herpetic neuralgia (PHN) and TN, respectively [34,35]. Both their randomized, double-blind, placebo-controlled, crossover studies showed that pain relief with topical application of lidocaine in PHN and TN patients was as seen in a significantly decreased VAS and NRS, respectively [34,35]. For patients with atypical odontalgia (AO) that is a possible orofacial neuropathic pain condition [36], List et al. evaluated the analgesic effect of lidocaine in a randomized, double-blind, placebo-controlled, crossover study [37]. The significantly lower VAS pain scores following lidocaine injections compared with placebo injections illustrated its effect in AO patients [37]. In the same manner, List et al. also examined the effect of topical anesthesia in healthy female subjects using lidocaine gel by assessing the QST and VAS [38]. Their study found no significant difference in pain thresholds and self-reported pain intensity between lidocaine and placebo [38], which is in line with the present results of the FPT and the NRS where the effect of topical lidocaine application did not differ significantly from placebo. Previously, Okayasu et al. reported a topical lidocaine-induced increase of the FPT in young symptom-free subjects [18]. Comparing the present result and the previous study of Okayasu et al. [18], experimental conditions were not completely identical. In both studies, all subjects were young symptom-free females, but the examiners and their gender were different (Examiners in the present and previous studies were M.T and I.O who are female and male, respectively). A previous study showed that subjects tolerate more pain when they are tested by an examiner of the opposite sex [39]. Based on this result in future studies, it is important to make all subjects and the examiner the same gender of female, and the same experiment in the patients with BMS should be done, comparing the results with those obtained in the present study in healthy female subjects, in the same way as List et al. did for patients with AO [37,38].

Topical lidocaine regularly appears effective in patients with neuropathic pain, especially if peripheral factors are more involved in the pathophysiology [34,35,37]. If in BMS patients a significant effect of lidocaine is found, it could suggest that its etiology is neuropathic. But if not, the pathophysiology for BMS might be ascribed to nociplastic pain that is neither a nociceptive nor a neuropathic pain condition [40].

Conflicts of Interest

The authors report no conflict of interest.

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