

The Effect of Topical Anesthesia on Jaw Pain Thresholds in Patients with Generalized Pain

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ABSTRACT

Chronic widespread pain and fibromyalgia often coexist with temporomandibular disorders (TMD) and affects mostly women. Studies have shown lower pressure pain thresholds (PPT) in these patients indicating that hyperalgesia is involved.

The aim for this study was to investigate the effect of topical anesthesia on PPT for jaw muscles in patients with widespread pain. The hypothesis was that the PPT in these patients would increase after applying topical anesthetic cream.

Ten women (aged 25-64 years, median: 50 years) diagnosed with TMD associated with widespread pain, reported from at least three different anatomical sites apart from the jaw region and pain to palpation according to the American College of Rheumatology criteria 1990, were included in the study. The double blind randomized trial was based on measurements of PPT with an Algometer before and after the application of anesthetic cream (EMLA) or placebo cream. The chosen measurement sites were the anterior part of the temporal muscle bilaterally, the belly of the masseter muscle bilaterally and the pollicis transversa muscle of the dominant hand. In the statistical analysis Wilcoxon's rank sum test was used and a P-value <0.05 was considered statistically significant.

There was a large inter-individual variation of PPT. No statistically significant differences in PPT-values before and after application of the EMLA or placebo creams were observed.

In conclusion, the study showed that application of topical anesthesia had no significant effect on PPT in patients with widespread pain. Mechanisms related to central sensitization may have contributed to this result.

INTRODUCTION

Palpation is a clinical examination method used to test whether pain and tenderness can be elicited from the palpated area and related structures (Hedenberg-Magnusson et al., 1997). When done manually, the examiner controls the pressure level and proportion with the fingertips (Buchgreitz et al., 2006). Pressure can also be applied with an Algometer where a more precise pressure level can be maintained and measured (Fredriksson et al., 2000). Pain to palpation over muscles may be interpreted as a sign of myalgia and pain elicited over a joint as a sign of arthralgia or arthritis. Response to palpation is thus a cornerstone in the diagnostic process of these conditions (Schiffman et al., 2014). Because of a fairly high sensitivity and reliability, palpation is therefore regularly used in the clinic (McMillan and Lawson, 1994).

Measurement of pressure pain thresholds (PPT) is used in clinical and experimental research on pain conditions including chronic widespread pain and fibromyalgia. PPT is defined as the minimum pressure needed to change a feeling of pressure into a painful sensation. For patients with chronic widespread pain and fibromyalgia, this sensation is evoked earlier than in healthy individuals, usually explained by the phenomenon hyperalgesia (Hedenberg-Magnusson et al., 1997; Lidbeck, 2007; Meeus and Nijs, 2007). Measurements of PPT can be helpful in understanding palpation, patient valuation and the mechanisms behind musculoskeletal pain. The validity for these measurements are based on differences in PPT between healthy individuals and those with temporomandibular disorder (TMD) (Ohrbach and Gale, 1989b).

TMD is a functional disturbance of the jaw system which includes pain and dysfunction in the temporomandibular joint, jaw muscles and associated structures (Okeson, 2013). Signs and symptoms of TMD vary between ages. TMD pain affects approximately 10 % of the adult population before retirement ages (Velly et al., 2010). The prevalence increases during adolescence, peaks in the middle age and then decreases. It is also more common among women (Yekkalam and Wänman, 2014). The influence of occlusion on TMD has been questioned to be an etiology, but the focus has shifted to biological, behavioral and psychosocial factors. The effect on signs and symptoms of

TMD by bruxism is also debated (Johansson et al., 2008). Therefore most advocate is a multifactorial etiology of TMD with risk factors such as depression, female gender and other pain conditions (Marklund and Wänman, 2010). TMD is usually mild to moderate in intensity and fluctuate over time (Marklund and Wänman, 2010; Velly et al., 2010). Co-morbidity between TMD and other chronic pain conditions, such as fibromyalgia, headache and neck pain, has been reported (Johansson et al., 2008). For some individuals TMD pain will progress to a chronic pain condition (Velly et al., 2010).

About 10 to 20 % of patients with TMD also have a chronic widespread pain condition (Plesh et al., 1996; Velly et al., 2010). Chronic widespread pain, also called generalized pain, is defined as musculoskeletal pain below and above the waist, bilateral in the extremities and with duration for at least three months according to the American College of Rheumatology (ACR) criteria 1990 (Cimmino et al., 2011). Another condition that is characterized by widespread pain is fibromyalgia. This condition affects approximately 2 % of the population and is also classified by the ACR criteria by a presence of widespread pain and the existence of at least 11 out of 18 tender points (Choy et al., 2009). Tender points are specific locations with low PPT and an increased hyper sensibility in muscles, tendons and ligaments (Fricton, 2004).

It has been suggested that men and women differ in how pain is interpreted and experienced. Compared to men, women report more severe pain, with a longer duration, and women are also at a higher risk of developing chronic pain conditions (Castro-Sánchez et al., 2012). There may be biological differences that could explain why there seem to be different pain perceptions between men and women as well as between individuals. One suggested factor is variations in sex hormone levels that modulate different types of pain. Another factor is differences in brain function involving thalamic and cortical interpretation of nociceptive stimuli that could affect the sensitivity (Castro-Sánchez et al., 2012). Genetic factors may also affect pain sensitivity (Castro-Sánchez et al., 2012). Non-sensory and non-biological factors such as anxiety and depression may affect pain experience and perception and are associated with more severe pain experiences. Furthermore, social factors may also affect the approach and expression which may result in fewer pain reports among men. Taken together, all these

factors in combination may explain a male to female ratio of 1:2-3 for prevalence of pain (Castro-Sánchez et al., 2012).

Pain may be elicited from both peripheral and central mechanisms. Pain of peripheral origin is most commonly related to local tissue injury (Fricton, 2004). The International Association for the Study of Pain (IASP) defines pain as “*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*” (Reinders et al., 2002). Pain has many different characteristics and patients with chronic widespread pain often describe their pain character as dull, throbbing and central (Fricton, 2004).

Trigeminal pain conditions can effect spinal pain and vice versa (Wiesinger et al., 2007). Temporomandibular pain may also enhance pain sensitivity and potentiate pain in other body regions (Vierck, 2006).

A theory about pain development in patients with widespread pain is that the pain impulse originates from deep tissues, such as muscles. If a genetic predisposition exists, these impulses could lead to a peripheral sensitization and neuroplastic changes of the central nervous system, which can result in central sensitization. When this occurs, a cascade reaction of transcriptional and translational events leads to an increased sensitivity (hyperalgesia/allodynia) in second or higher order neurons. It is still uncertain why these changes have a long duration and are permanent in fibromyalgia patients with chronic widespread pain (Staud, 2011).

Central sensitization can be caused by a continued stimulus of the nociceptive neurons in the spinal cord. The stimulus can be frequent or persistent. The reaction is normally reversible if the peripheral nociception is discontinued, but if not, may lead to chronic pain (Lidbeck, 2007). Central sensitization can thus result in allodynia (pain caused by a normal non-painful stimuli) and hyperalgesia (increased response to normal painful stimuli) (Lidbeck, 2007). Muscle palpation as a diagnostic method in patients with hyperalgesia has thus not been fully investigated.

The aim of this experimental study was therefore to investigate if the PPT-level increased after application of topical anesthesia to the skin over the jaw muscles in patients with chronic widespread pain. Thus concluding that there are peripheral

mechanisms behind the hyperalgesic effect in these patients. The hypothesis was that the PPT-level in patients with TMD and chronic widespread pain increases after application of topical anesthetic cream.

MATERIAL AND METHODS

Study-population

Ten subjects (aged 25-64 years, median: 50 years) participated in the study. The inclusion criteria were women, diagnosed with TMD pain associated with pain reported from at least three different anatomical sites outside the jaw region and pain to palpation at thumb, arm and calf muscle sites. The reported pain in the jaw region should be stated as four or more on an 11-point numerical rating scale (NRS) with the end points “no pain at all” to “maximal and unbearable pain”. The subjects were instructed to not consume alcohol or painkillers 24 hr before the examination.

Methods

Before entering the study, eligible subjects were examined by specialists in Clinical Oral Physiology to ensure that the inclusion criteria were fulfilled. They were informed about the study and were included if they gave informed consent. They filled out a short questionnaire including current medicine intake. The study was approved by a local ethical committee.

All of the participants were included in the study. One participant had Gabapentin 17 hr before, one Paracetamol 500 mg, 12 hr before and another one Ibuprofen 500 mg, 20 hr before the examination. Since the half time of these medications was a couple of hours after the intake, we decided to include all participants.

The chosen sites for the study were the anterior part of the temporal muscles (right and left side), the center part of the masseter muscles (right and left side) and a thumb muscle; the pollicis transversa muscle, on back of the dominant hand (Fig. 1). The thumb muscle was used as an extra trigeminal reference site. The order of measurements for each subject was randomized before the experiment using SPSS v21.

PPT was measured with an Algometer (Somedic) using a handheld probe, held against the muscle site with an increasing pressure according to the manufacturers' instruction.

The probe used for this study had an area of 1 cm². The Algometer was set for an increasing pressure of 30 kPa/sec, with a minimum pressure of 10 kPa and maximum 500 kPa. The subjects were instructed to push a button as soon as they perceived the applied pressure as painful.

The trial had a double-blind experimental design and was carried out with the patient sitting in a stable chair with a backrest. Investigator B marked the five test sites with a ball-pen to minimize the error of the site locations. After a comprehensive explanation of how the Algometer works, a trial test was performed on the pollicis transversa muscle on the non-dominant hand to demonstrate the experiment procedure. Investigator B then did three measurements per site according to the randomized order.

Investigator B then left the room and investigator A applied either EMLA (AstraZeneca, Sweden) or placebo-cream (a regular perfume free skin lotion with the similar texture and color as EMLA, Liv by Lahega Kemi AB, Sweden) to the respective sites in randomized order. EMLA consists of lidocaine (25 mg/ml) and prilocaine (25 mg/ml) as active substances. EMLA was added to either the left or the right muscle site. The thumb either had EMLA or placebo cream. The cream was applied to the skin with cotton with the help of a template with the diameter of 2 cm² and was left on the skin for 5 min. Before Investigator B returned into the room, investigator A wiped off the creams with separate gauzes for each site. Investigator B then repeated the measurements, three times on each site, with the same randomized order as for the baseline recording.

Ethical considerations

Oral and written information about the study was given to the participants both at the recruiting examination and on the day of the trial. The information included a brief summary of the procedure, overall aim and the advantages/disadvantages of participating in the study. They were also informed that they at any time could discontinue the experiment and that their identity would be anonymous in the data. The participants gave their written informed consent to the experiment on the day of the experiment before the trial. A remuneration of 200 SEK was given to all the participants to compensate for the time (0.5 hr). The ethical considerations were related to the pain elicited by the Algometer. The subjects were instructed to react on the first perception

of pain and had thus full control over the experimentally induced pain. The experiment only involves short lasting low-grade pain with no risks or side effects. There was a possibility that the palpated sites got sensitized after the measurements, but because of the low pressure, the risk for sensitization over a longer period of time was considered to be low. The benefit from the study for the patients can relate to the interpretation of elicited pain to palpation or other pressure to local spots.

The data from the experiments belong to the department of Clinical Oral Physiology, Umeå University, and will be stored together with the consent forms for ten years.

Literature search

The first scientific articles were provided to us from our tutors. In addition we performed a PubMed literature search using the following MeSH terms in different combinations; Algometer, characteristics, chronic widespread pain, definition, diagnosis, differences, epidemiology, etiology, fibromyalgia, jaw muscle, masseter, muscle, pain, pressure pain threshold, prevalence, relationship, temporalis, temporomandibular disorders, temporomandibular muscle and joint pain, widespread pain. Only a limited number of articles were retrieved in the multiple searches, approximately 20 per search. The majority of the articles concerned fibromyalgia. Since fibromyalgia is a part of chronic widespread pain, we decided to include all these articles. Many of the articles were about widespread pain in combination with other conditions, which was deemed irrelevant for our study and thus excluded. The searches gave us a repetition of articles with the same subject, but explained in different ways. The titles and abstracts were screened to identify the most appropriate articles, which were then included.

Statistical methods

During the experiments, data was stored in Somedic software and then transferred to an Excel document. The data was later transferred to SPSS v21 where the statistical calculations, analysis and figures were made. The data is presented as mean-values of the three measurements for each muscle site before and after appliance of the creams, and standard deviation (SD). Statistical analyses were done with a Wilcoxon signed rank test to analyze the difference in PPT-values before and after placement of the creams. Differences between sites at baseline were tested with Mann-Whitney U test for

independent samples. The temporal and masseter muscle sites were pooled. A P-value <0.05 was considered statistically significant.

RESULTS

PPT-values at baseline and after the application of placebo or EMLA cream for the tested sites are presented in Table 1. The PPT-values were significantly higher over the temporal ($P= 0.03$) and pollicis transversa muscle sites ($P < 0.001$) compared to the masseter muscle sites. No statistically significant differences in PPT-values before and after application of EMLA or placebo cream were observed (Fig. 2) except for the masseter muscle after application of placebo cream ($P < 0.05$). The intra-individual differences for the masseter and temporalis muscle sites before and after EMLA or placebo cream are presented in Figure 3. For the pollicis transversa muscle, there were no significant differences in the PPT-level between the participants in the placebo- and in the EMLA-groups, or before and after the application of the placebo and EMLA cream, respectively.

DISCUSSION

The main result from this study was that topical anesthesia, applied for 5 minutes to the skin of the palpation area, did not affect the PPT-levels in patients with chronic widespread pain and our hypothesis was thus rejected.

The mean PPT-values were similar to a previous study of the masseter muscle (Ernberg et al., 2000) but was lower than reported from spinally innervated regions (Castro-Sánchez et al., 2012) in fibromyalgia-patients. The PPT-values of the trapezius muscle in the latter study were approximately 3.6 kg/cm^2 . After converting our values into kg/cm^2 the mean values varied between $1.0\text{-}2.1 \text{ kg/cm}^2$ for all sites at baseline. In the study by Ernberg et al (Ernberg et al., 2000) the mean sum (left and right side of masseter muscle) of the PPT-value was 216 kPa based on 12 female fibromyalgia-patients. These results may indicate that spinally innervated sites have higher PPT-levels than trigeminal innervated sites. The study showed that the mean PPT-levels varied between the different muscle groups. This is supported by previous studies and indicates generally different PPT-levels in different innervated areas. It has been observed that temporal muscle sites have higher PPT-levels than masseter (McMillan and Lawson, 1994), which is in line with our results (Table 1). The reason for this

difference between sites is uncertain, but probably related to differences in the density of mechanoreceptors in the tested sites. It is known that the anatomy of the elevator muscles is complex with muscle fibers in a net with the connective tissue. This formation is associated with the muscle compliance and thus the variation of the PPT-levels (McMillan and Lawson, 1994).

One participant was an outlier with regard to the PPT-values which affected the standard deviation. A sub analysis, with the deviant participant excluded, resulted in more homogenous PPT values for the group and the significant difference in PPT after application of placebo cream in the masseter muscle also disappeared. One participant may thus have affected the results and should be considered a possible source of error because of her overall significantly higher PPT-values compared to the rest of the study-population (fig. 3).

As an extra-trigeminal site, we chose to measure the pollicis transversa muscle of the thumb, which has been demonstrated to be a similar tissue as masseter and temporalis (Kosek et al., 1993). Kosek showed in her study that there were no differences in PPT-levels within the same area in muscle bellies and bony areas in healthy individuals. She also showed that there were differences in the PPT-level within the same tissue in similar body regions which was proposed to be related to local differences such as skin sensitivity for palpation (Kosek et al., 1993).

A considered source of variation in PPT-levels is whether the tests are performed in a relaxed muscle position, as pain sensitivity of muscles varies between different activities. McMillan (McMillan and Lawson, 1994) studied how the PPT-level was affected when the temporalis and masseter muscles were in function, for example during tooth clenching (McMillan and Lawson, 1994; Ohrbach and Gale, 1989a). List et al (List et al., 1989) measured the PPT-level in the muscles in a relaxed position without tooth contact. In these measurements, the Algometer were in pressuring contact not only with the muscle belly, but also with tissues such as skin, fascia, nerves, blood vessels and jawbone. These structures altogether could therefore have affected our PPT-values (List et al., 1989). All our measurements were carried out in a relaxed position and thus the low PPT-level results could have been affected by the sensitivity of the periost and other tissues.

A manual palpation pressure with the fingertips may be more valid compared to the pressure produced by an Algometer. This since the fingers are steered by the examiner into the right position and the force is stable. But this technique instead lacks good reliability (List et al., 1989). We wanted to use a reliable measurement in our study and therefore chose to use a modern type of digital Algometer. The advantage of a digital Algometer is that the registered measurements can be calculated and compared statistically (List et al., 1989). Studies have shown that the first measurements with the Algometer usually shows higher PPT-values and therefore, it has been recommended to measure the PPT-level several times to achieve a mean PPT-value (Fredriksson et al., 2000). We chose to perform three measurements and calculate a mean value to increase the reliability. If we had increased the number of measurement even more, for example to five measurements, the reliability may have increased further (Fredriksson et al., 2000), but it might also have sensitized the sites.

Earlier studies with PPT-measurements have shown that there are differences in the PPT-level depending on the measuring speed and size of the probe (McMillan and Lawson, 1994). The probe size in our study, 1 cm², within the range of probes between 0.5 cm² and 2 cm², is a common size of probe in the facial area. The maximum limit of 500 kPa was chosen since the PPT-level for patients with generalized pain are lower than in healthy individuals, 426 kPa in healthy individuals compared to 216 kPa in fibromyalgia patients (Ernberg et al., 2000).

Our measuring speed of 30 kPa/sec was lower than in some previous studies that used 50 kPa/sec (McMillan and Lawson, 1994). This was chosen since the reaction time for the participants always will cause a delay in pressing the stop button. A lower measuring speed makes the increased PPT from the delay more reduced than when using a higher speed, but measuring speed can still not be excluded as a source of error. It is also difficult to maintain a constant application force on the palpation site when measuring with and Algometer, which could also be a contributing source of error to misleading PPT-values in our study.

Application of topical local anesthesia can have different effects depending on the application site, application time and the individual. A large variability in the analgesic effect of EMLA in the facial region has been suggested to be related to differences in

the local blood flow. The analgesic effect of EMLA may therefore decrease faster in the facial region since the blood flow is higher there compared to the dorsum of the hand (Nielsen et al., 1992). It can thereby not be excluded that differences in local blood flow could have affected our results and gave the impression of maintaining high PPT-values on the dominant hand compared to the facial region. According to the medical instruction, EMLA is recommended to be applied for at least 1 hour to achieve full anesthetic effect, but this recommendation relates to needle sticks (FASS : förteckning över humanläkemedel. 2013, 2013). The cream was only applied for 5 min in our study since we wanted to avoid effect on the deeper muscle nociceptors. It can therefore not be excluded that the lack of effect from the EMLA may be due to a short duration of application.

Another interesting observation in our experiment, after applying the creams, was a clear anticipation among the participants. They seemed to think that a change in pain perception would appear. Therefore, one consideration was whether this affected the response and thereby the PPT-level. Looking at the significant difference after application of placebo on masseter, this may therefore be one explanation to the increased PPT-values and the significant change (Huber et al., 2013).

Although we had instructed the participants to avoid medication for 24 hr before the trial, two of the participants had taken medication. Alvedon (active substance paracetamol) has a duration of 4.5 hr and an effect of 8 hr. Since the time spent before taking Alvedon exceeds 8 hr we concluded that this would not have affected our test results. Gabapentin (active substance gabapentin) is an antiepileptic and also used as treatment for peripheral neuropathic pain. The half time for 400 mg, which our participant had taken, is about 11 hr and we therefore do not think this influenced our results. Ipren (active substance Ibuprofen) has a half time of 2 hr and is almost completely eliminated within 24 hr. We can thereby not exclude that Ipren could have influenced the PPT-values for participant number 5. (Fig. 2) (FASS : förteckning över humanläkemedel. 2013, 2013).

In conclusion, this experimental double blind study shows that application of topical anesthesia (EMLA) for a 5-minute duration does not significantly affect PPT-levels in patients with chronic widespread pain. The study also showed low PPT-levels which

complies with other studies (Ernberg et al., 2000). Whether a lower pressure should be used when diagnosing women with chronic widespread pain for TMD or not, can still not be concluded. Looking at widespread pain in a broad perspective it is important to remember that the cause of generalized pain is still not fully understood and lacks a clear etiology (Staud and Domingo, 2001). More research is needed for patients with widespread pain in order to improve both diagnosis and treatment.

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Table 1. Mean values and standard deviation (SD) of pressure pain threshold (PPT) for temporal, masseter and the dominant thumb muscle, pollicis transversa, before and after PLACEBO and EMLA among 10 women with TMD pain associated with generalized pain.

Site	Baseline Mean (SD)	PLACEBO Mean (SD)	P-value
Temporal m.	139.4 (83.9)	123.5 (52.0)	0.29
Masseter m.	95.7 (43.5)	113.8 (41.6)	0.047
Pollicis transversa	130.0 (24.3)	148.1 (18.6)	0.29
Site	Baseline Mean (SD)	EMLA Mean (SD)	P-value
Temporal m.	141.5 (95.8)	140.8 (76.4)	0.72
Masseter m.	100.0 (35.1)	111.6 (36.0)	0.14
Pollicis transversa	205.1 (76.3)	221.9 (76.3)	0.40

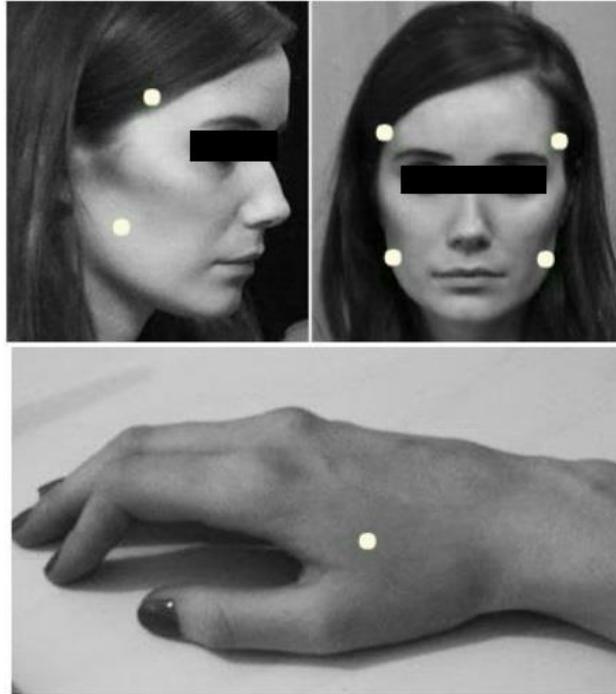


Figure 1. The anterior part of the temporal muscles (right and left side), the center part of the masseter muscles (right and left side) and one of the thumb muscles, pollicis transversa, on back of the hand.

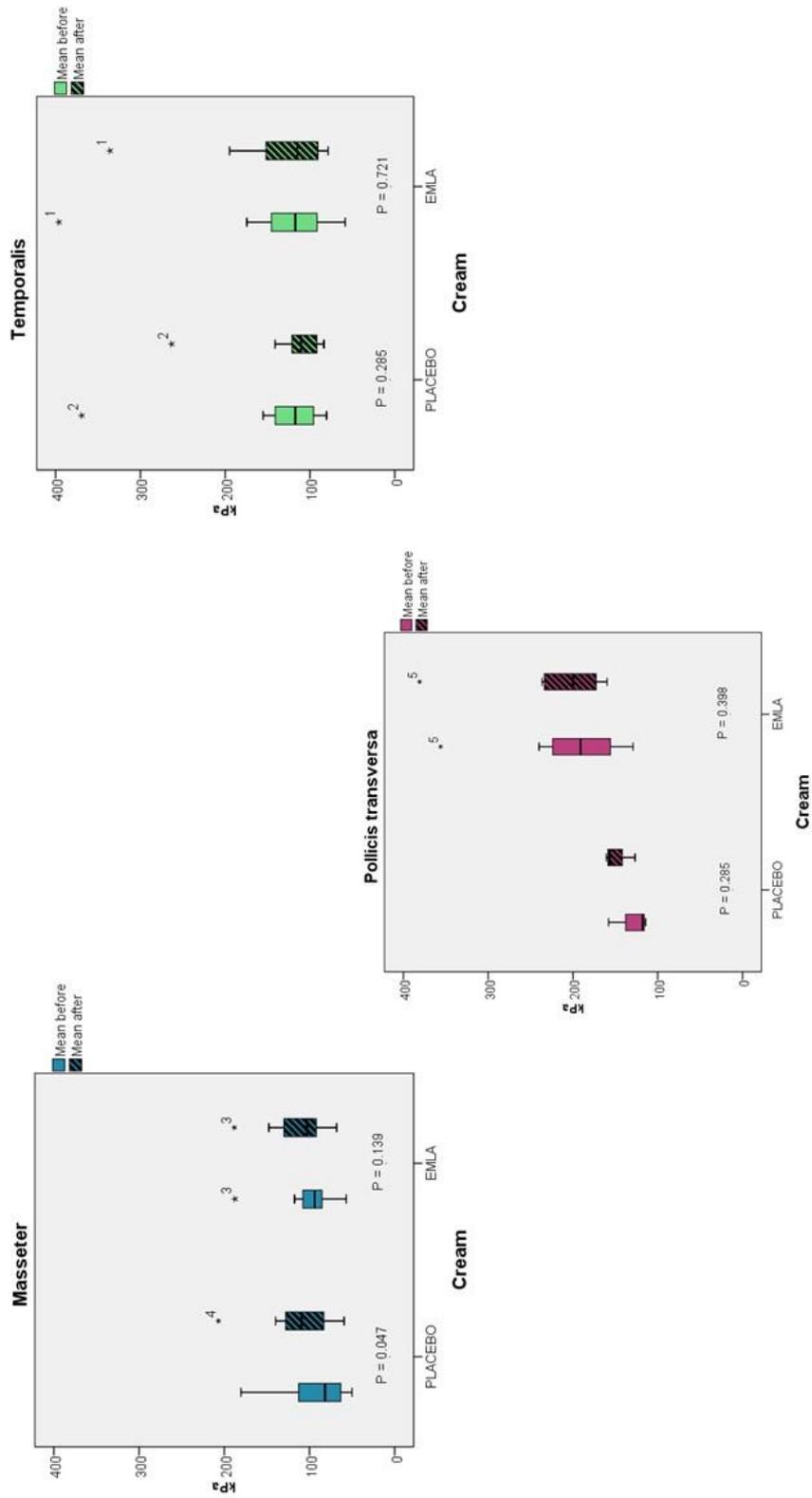


Figure 2. Box plots showing pain pressure thresholds in kPa before and after application of topical anesthesia (EMLA®) or placebo cream for 5 min of the temporal (A) the masseter muscle site (B) and the dominant thumb (C) in 10 women with TMD pain associated with generalized pain.

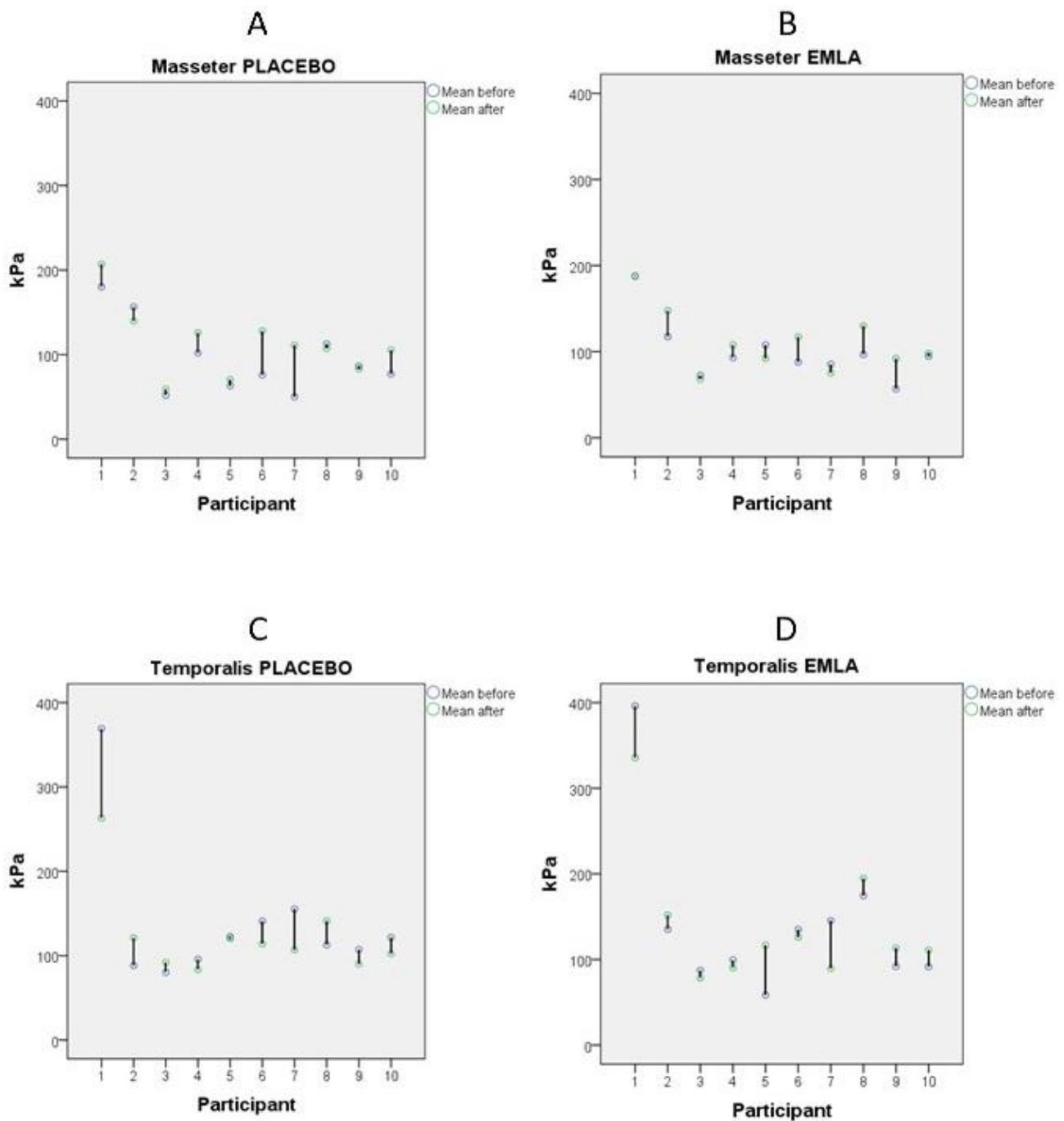


Figure 3. The individual mean pressure pain threshold (PPT) value in kPa before and after applying placebo and EMLA cream for the respective muscle sites; (A) seven decreasing and three increasing PPT-levels for the temporal muscle after applying placebo; (B) five decreasing and five increasing PPT-levels for the temporal muscle after applying EMLA; (C) three decreasing and seven increasing PPT-levels for the temporalis muscle after applying placebo; (D) three decreasing and seven increasing PPT-levels for the masseter muscle after applying EMLA.