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ORIGINAL ARTICLE

The analgesic efficacy of lidocaine/prilocaine (EMLA) cream during fine-needle aspiration biopsy of thyroid nodules

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Summary

Objective Pain is one of the few drawbacks of fine-needle aspiration biopsy (FNAB) in patients with nodular thyroid disease (NTD). Lidocaine/prilocaine cream, an eutectic mixture of local anaesthetics (EMLA), is a frequently used topical anaesthetic. Despite its well-documented efficacy for the relief of pain associated with other cutaneous procedures that involve needle insertion, the analgesic role of EMLA has not been previously reported in patients with NTD who are undergoing FNAB. The aim of this study was to determine the analgesic efficacy of EMLA for FNAB-associated pain in patients with NTD.

Design Double-blind, placebo-controlled clinical trial.

Patients The study was conducted at a thyroid outpatient clinic. We studied 99 patients with NTD.

Measurements Patients with NTD were allocated to receive either 2·5 g of EMLA ($n = 50$) or placebo ($n = 49$) 60 min before ultrasonographically guided FNAB. A series of four biopsies of each nodule was performed. Patients rated pain associated with the procedure according to a 100-mm visual analogue scale (VAS), an 11-point numeric rating scale (NRS), and 4-category verbal rating scale (VRS).

Results When the EMLA group was compared with the placebo group, there were no significant differences with respect to age, sex, thyroid volume, nodule size or nodule site. Significant differences were noted in the pain ratings of the two groups according to all three pain scales. When the effectiveness of EMLA was compared with that of placebo, the mean VAS score was 25·0 ± 22·3 mm *vs.* 40·0 ± 30·5 mm ($P = 0·006$) and the mean NRS score was 2·9 ± 2·3 points *vs.* 4·0 ± 2·6 points ($P = 0·02$). The absolute numbers according to VRS score in each group was also significantly different ($P = 0·01$). Although our sample size was small, the data suggest that FNAB-associated pain was sex-related and that women were significantly more sensitive than were men ($P = 0·003$ for VAS score and $P = 0·001$ for NRS score). No adverse effects from the use of EMLA were reported.

Conclusions To our knowledge, this is the first study demonstrating that a topical anaesthetic, EMLA, provides an effective and non-invasive analgesia during the FNAB of NTD.

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Introduction

In patients with nodular thyroid disease (NTD), fine-needle aspiration biopsy (FNAB) has long been established as an effective, reliable and safe procedure. FNAB often causes minor discomfort and slight temporary pain, and the use of a local anaesthetic is usually not recommended.[1] However, some patients experience severe and excruciating pain during FNAB. An eutectic mixture of local anaesthetics (EMLA) is a combination of lidocaine 2·5% and prilocaine 2·5% that is frequently used as a topical anaesthetic. Eutectic means a mixture of two or more substances whose melting point is lower than that of any of the constituent. Most studies have established that EMLA is an effective agent for reducing pain associated with cutaneous procedures that involve needle insertions, such as venipuncture, intravenous catheter placement, transrectal biopsy, dermal instrumentation and lumbar puncture.[2–6]

The evidence for the efficacy of EMLA in the literature prompted us to consider its use in decreasing the pain associated with the FNAB of thyroid nodules.

Patients and methods

This double-blind, placebo-controlled clinical trial was conducted at a thyroid outpatient clinic. The Baskent University Ethics Committee for Human Studies approved the protocol. All participants provided informed written consent. Ninety-nine consecutive nodular thyroid disease patients (age range 27–78 years) biopsied for the first time between April and September 2006 were enrolled at the Thyroid Center of Baskent University Faculty of Medicine in Ankara, Turkey. Ultrasonography examination was performed a few days before the FNAB procedure. We hypothesize that as the number of biopsy attempts increase, perceived pain scores significantly change. Newly diagnosed patients with NTD requiring only one

biopsy were included to obtain a uniform study population. All patients had nodule sizes of 1 cm or more and normal TSH levels. Patients with altered mental status or an inability to comprehend questions, a history of long-term opioid or analgesic use, or allergy to the trial drug were excluded.

Patients were allocated hospital identification numbers by a computer-based system. Those assigned an even number were allocated to the local anaesthetic arm of the study, whereas those assigned an odd number were allocated to the placebo arm. The creams were applied by a nurse who was not blinded with regard to the kind of allocation and not involved in the biopsy procedure.

The placebo cream consisted of a white lotion that is similar in consistency to EMLA cream. To each subject, either EMLA 5% cream (Astra Zeneca, Istanbul, Turkey) in a dose of 2·5 ml (~2·5 g) or a similar amount of placebo cream was uniformly applied in a thick layer over the nodule selected for FNAB 60 min before the procedure was performed. The endocrinologist performing the FNAB was not involved in the application of the creams. Thus, neither the patient nor the endocrinologist knew which cream had been applied. Just before needle insertion, the cream was wiped off by the study nurse, and the endocrinologist was called to perform the FNAB, which for each patient was completed in 15 min. According to the standard practice at our institution, four aspirations were made with four different 25-gauge needles at different sites in each nodule. The same endocrinologist (AG) performed all ultrasonographically guided FNABs by means of a 10-MHz linear probe (Logiq 5 Pro, GE Medical Systems, WI, USA). Immediately after the completion of the FNAB, each patient was transferred to another room. An endocrinology fellow instructed the patient in the completion of a pain survey form in which the patient was asked to rate his or her pain according to the following three pain rating scores:

1 A horizontal 100-mm visual analogue scale (VAS) anchored with the words 'no pain' on the left border and 'worst possible pain' on the right border. Patients were asked to make a mark on the line that represented their pain intensity, and the VAS was scored by measuring the distance from the 'no pain' end of the line.

2 A horizontally depicted 11-point numerical rating scale (NRS) that ranged from 0 to 10, with 0 representing 'no pain' and 10 representing the 'worst pain imaginable.' Patients were asked to mark the number that best represented the pain they experienced during the procedure.

3 A four-point verbal rating scale (VRS) in which a score of 0 represented no pain; 1, mild pain; 2, moderate pain; and 3, severe pain.

As previous studies have shown, category scales for pain intensity classify a VAS score of 0–4 mm as no pain; 5–44 mm as mild pain, 45–74 mm as moderate pain; and 75–100 mm as severe pain. An NRS score of 1–4 indicates mild pain; 5–6, moderate pain; and 7–10, severe pain.[7,8]

Statistical analysis

All continuous data were expressed as means ± SD. Data were analysed with SPSS software (Statistical Package for the Social Sciences, version 11·0, SSPS Inc, Chicago, IL, USA). Differences in baseline characteristics between patients and controls were assessed by means of the Student *t*-test for continuous variables. An independent-samples *t*-test was conducted as a nonparametric to determine whether there was a significant difference in pain scores between the two groups of patients. The absolute numbers according to VRS score in each group was compared with χ^2-test. It was calculated that approximately 30 patients were necessary in each treatment group to achieve a 90% power of detecting a 20 mm difference on the visual analogue scale between groups. *P*-values of less than 0·05 were considered statistically significant.

Table 1. Patient characteristics and pain scores: EMLA *vs.* placebo during the fine-needle aspiration biopsy of thyroid nodules

	EMLA ($n = 50$)	Placebo ($n = 49$)	*P*-value
Female/male	6/44	8/41	> 0·05
Age (years)	51·6 ± 11·1	46·8 ± 13·1	> 0·05
Nodule size (mean ± SD) (mm)	20·7 ± 10·9	18·5 ± 5·8	> 0·05
Thyroid volume (ml)	21·6 ± 9·2	22·4 ± 11·9	> 0·05
VAS (mean ± SD)	25·0 ± 22·3	40·0 ± 30·5	0·006
NRS (mean ± SD)	2·9 ± 2·3	4·0 ± 2·5	0·02
VRS (*n*)			0·01
No pain	9	4	
Mild pain	26	16	
Moderate pain	11	14	
Severe pain	4	15	

EMLA, lidocaine/prilocaine; SD, standard deviation; VAS, visual analogue scale; NRS, numerical rating scale; VRS, verbal rating scale.

Results

A total of 99 consecutive patients participated in the study. The patients who were studied were assigned to one of two groups and were comparable with respect to age, sex, thyroid nodule size and volume, and nodule site (Table 1).

As shown in Table 1, the mean VAS score was 25·0 ± 22·3 in the EMLA group and 40·0 ± 30·5 in the placebo group ($P = 0·006$). The mean NRS score of the EMLA group (2·9 ± 2·3) was also significantly lower than that of the placebo group (4·0 ± 2·5; $P = 0·02$). In addition, the absolute numbers according to VRS score in each group was significantly different ($P = 0·01$).

Category scales for pain intensity was presented in Table 2. The percentage of patients with 'no pain' or 'mild pain' in the EMLA group was significantly higher than that in the placebo group ($P = 0·001$). Similarly, the percentage of patients with 'moderate-to-severe pain' in the placebo group was significantly higher than that in the EMLA group ($P = 0·001$).

Despite the fact that few male patients ($n = 14$) were evaluated in this study, the significantly higher pain scores in the female patients (35·7 ± 27·6 for VAS, 3·8 ± 2·5 for NSR), as opposed to the male patients (12·8 ± 17·9 for VAS, 1·5 ± 1·7 for NSR) (male *vs.* female, $P = 0·003$ for VAS and $P = 0·001$ for NSR) were a feature of interest. Except for one male patient, none of the other male patients had a pain score in the moderate-to-severe intensity range.

No adverse effects from the application of EMLA were observed.

Table 2. Analgesic efficacy of EMLA *vs.* placebo during the fine-needle aspiration biopsy of thyroid nodules

	Category scales for pain intensity (%)							
	EMLA ($n = 50$)				Placebo ($n = 49$)			
	No pain	Mild pain	Moderate pain	Severe pain	No pain	Mild pain	Moderate pain	Severe pain
VAS	26	58	12	4	14	43	25	18
NRS	16	64	14	6	6	53	16	25
VRS	18	52	22	8	8	33	29	30
VAS pain scale 0–4 mm, no pain 5–44 mm, mild pain 45–74 mm, moderate pain 75–100 mm, severe pain					NRS pain scale Zero, no pain 1–4, mild pain 5–6, moderate pain 7–10, severe pain			

EMLA, lidocaine/prilocaine; VAS, visual analogue scale; NRS, numerical rating scale; VRS, verbal rating scale.

Discussion

FNAB is an indispensable diagnostic tool in the management of thyroid nodules. Although FNAB is safe, simple, cost-effective, reliable and generally well-tolerated, some patients complain of pain and discomfort during the procedure.[1] Individuals with a phobia of needles or of experiencing pain may find FNAB distressing or unbearable, and performing the procedure on those patients can be technically difficult for the physician. The routine use of any form of local anaesthetic is not usually recommended, but some patients who experience extreme discomfort during FNAB often request a nonpainful, effective and noninvasive topical anaesthesia.

Clinical practice has recently begun to incorporate various techniques for decreasing the discomfort and pain of procedures involving routine needle punctures, such as venipuncture, intravenous catheter placement and lumbar puncture. EMLA cream, an effective topical anaesthetic, is frequently applied to minimize such procedural pain.[2–6] We have evaluated the potential use of EMLA cream as a local anaesthetic for the management of pain associated with the FNAB of thyroid nodules.

Pain is a subjective sensation and is therefore difficult to measure. Pain assessment scales are useful for eliciting responses from patients about their pain or discomfort and are frequently used to quantify the intensity of perceived pain during interventional procedures. The relative merits of the three pain scales (VAS, NRS and VRS) often used to assess pain have been well studied, and their usefulness has been validated by several investigators.[8,9]

Our results show that the use of EMLA before FNAB significantly reduced the intensity of pain during that procedure and was more effective than placebo according to patients' assessments on all three pain scales. The percentage of patients in the placebo group who experienced moderate-to-severe pain was about three-fold that of the EMLA group.

Although the size of our study sample was too small to render a definite conclusion possible, we noted the tendency of male patients to feel less pain and discomfort than did female patients in both the EMLA and placebo groups. Sex-related differences in the perception of pain intensity have been previously identified.[10] It has been shown that women have a lower pain threshold, a greater ability to discriminate pain, higher pain ratings and less tolerance of noxious stimuli than do men.[11,12] Women also have been shown to have lower cold pressor pain thresholds and pain tolerance levels and to report greater sensory pain than do men. The authors suggested that women reported more negative pain experiences than did men. The influence of sex hormones on the neurochemical mediation of analgesia has also been discussed in the literature.[10]

Some obstacles with the use of EMLA as an effective and practical topical anaesthetic in patients undergoing the FNAB of a thyroid nodule may be present, however. Although EMLA application significantly reduced perceived pain intensity in our study, it did not provide complete analgesia during the procedure in most of the patients. We suggest that the application of EMLA may not have penetrated to the depth required for complete analgesia. In addition, EMLA requires a minimum application time of at least 1 h to produce effective topical anaesthesia, which may render its use impractical in a busy clinic. However, allowing a nurse to apply the cream before the patient enters the biopsy room might obviate that disadvantage.

There are several limitations related to our study design that should be discussed. First, our study primarily investigated the efficacy of EMLA as a topical anaesthetic and was not originally designed to investigate the predictors of pain relief. Thus we did not measure or consider a number of additional factors that may have contributed to the patients' pain ratings. Future research examining the predictors of pain (such as the patient's level of anxiety or depression), which were not assessed in this study, would clarify that issue. In addition, our study sample was overwhelmingly female. Expansion of the study to include additional male patients would help to determine whether our results apply to both sexes.

The efficacy of topical anaesthetics in patients undergoing FNAB for diseases other than thyroid nodules has been reported by several other authors.[13,14] Our findings indicated that EMLA is a safe and effective analgesic agent. To our knowledge, this is the first report studying the effectiveness of a local anaesthetic in the management of pain associated with FNAB in patients with NTD.

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