

## Techniques

# Needle-Free Delivery of Lidocaine for Reducing the Pain Associated with the Fine-Needle Aspiration Biopsy of Thyroid Nodules: Time-Saving and Efficacious Procedure

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**Objective:** Fine-needle aspiration biopsy (FNAB) is a mandatory procedure in evaluation of thyroid nodules. However, it is sometimes perceived as a painful procedure by the patients. Efficacy of the needle-free injection of local anesthesia for reducing the pain associated with other cutaneous procedures that involve needle insertion was previously reported. In this double-blind, placebo-controlled clinical trial, we evaluated the effectiveness of a needle-free injection of lidocaine in achieving satisfactory pain control in patients undergoing FNAB of thyroid nodules. **Design:** Patients were allocated to receive either lidocaine administered by needle-free injection system ( $n = 55$ ) or placebo (isotonic saline) ( $n = 52$ ) 2–3 minutes before FNAB. A series of four aspirations of each nodule was performed. The patients rated pain associated with the procedure according to a 100-mm visual analog scale (VAS), an 11-point numeric rating scale (NRS), and a four-category verbal rating scale (VRS). **Main outcome measure:** The two groups studied were similar with respect to age, sex, thyroid volume, nodule size, and nodule site. When the effectiveness of lidocaine was compared with that of placebo, the mean VAS score was  $11.4 \pm 13.6$  mm versus  $38.2 \pm 35.5$  mm ( $p < 0.0001$ ) and the mean NRS score was  $1.4 \pm 1.5$  points versus  $3.9 \pm 2.6$  points ( $p < 0.0001$ ), respectively. The absolute numbers according to VRS score in each group was also significantly different ( $p < 0.0001$ ). The percentage of patients with “no pain” or “mild pain” in the lidocaine group (90.9%) was significantly higher than that in the placebo group (44.2%) ( $p < 0.0001$ ). Less than 10% of the patients in lidocaine group experienced moderate pain and none experienced severe pain. No adverse treatment-related effects were observed. **Conclusions:** To our knowledge, this is the first study demonstrating that the needle-free delivery of lidocaine is an effective, useful, and noninvasive method of providing local anesthesia for the FNAB of thyroid nodules.

### Introduction

**F**INE-NEEDLE ASPIRATION BIOPSY (FNAB) is an effective, reliable, safe, and mandatory diagnostic procedure for the evaluation of thyroid nodules. FNAB is associated with minor discomfort and slight temporary pain that are easily well tolerated by most patients, and the routine administration of any form of local anesthetic before the procedure is not usually recommended (1,2). However, some patients (especially those who are pain phobic) perceive FNAB as a frightening and stressful procedure, and those individuals often request a nonpainful, effective, and noninvasive topical anesthetic (2).

Pain control is a concern during every cutaneous invasive procedure. Eutectic mixture of local anesthetics (EMLA) cream, which consists of a combination of lidocaine 2.5% and prilocaine 2.5%, has been shown to provide effective local anesthesia for the FNAB of thyroid nodules (2). In a study by Gursoy and colleagues (2), the application of EMLA significantly reduced patients' perceived pain intensity but did not provide complete analgesia during FNAB in most of the subjects (perhaps because that cream did not penetrate to the depth required for complete analgesia). However, EMLA must be applied a minimum of 1 hour before FNAB to provide effective topical anesthesia, and that disadvantage may render its use impractical in a busy clinic (2).

The needle-free system of local anesthetic administration is a pneumatically powered pain-free injection system that delivers medications either intradermally or subcutaneously. The needle-free system enables the noninvasive, nontraumatic, and infection-free administration of a local anesthetic that provides a rapid onset of analgesia and causes less pain than that produced by a needle-stick. It has been successfully used among patients undergoing venipuncture, intravenous catheter insertion, cutaneous biopsy procedure, and vaccination (3–8) and for the administration of insulin and human growth hormone (9–11). Our study was undertaken to evaluate the efficacy of the needle-free delivery of lidocaine for the rapid production of local anesthesia before FNAB.

### Materials and Methods

This was a single-center, randomized, double-blind, placebo-controlled, single-dose, parallel-group study in patients with one or more thyroid nodules who were scheduled to undergo FNAB. The Baskent University Ethics Committee for Human Studies approved the protocol. All participants provided informed consent. One hundred seven consecutive patients (age range, 16–81 years) with nodular thyroid disease who underwent FNAB at the Thyroid Center of Baskent University Faculty of Medicine in Ankara, Turkey, between August 2006 and December 2006 were enrolled in the study. Newly diagnosed patients with one or more thyroid nodules requiring only one biopsy were included to obtain a uniform study population, because we assumed that as the number of biopsy attempts increased, perceived pain scores would significantly change. All patients had a nodule size of 1 cm or more and a level of thyrotropin within normal limits. Patients with any of the following characteristics were excluded from the study: altered mental status or an inability to comprehend questions, a history of long-term opioid or analgesic drug use, an allergy to the trial drug, atrophic or fragile skin resulting from long-term steroid use, extreme old age, or a bleeding disorder such as hemophilia or anticoagulation. Patients were allocated by a hospital identification number assigned via a computer-based system. Patients assigned an even number were allocated to the local-anesthetic arm of the study, and those with an odd number were allocated to the placebo arm.

The needle-free system used was the Injex needle-free medication delivery system (Rösch Medizintechnik, Berlin, Germany), which has been approved by the U.S. Food and Drug Administration (FDA) for the administration of subcutaneous injections (Fig. 1). The Injex needle-free medication delivery system consists of the following components: 1) reusable, pen-sized stainless steel jet injector; 2) compact reset box acting as carrying case and reset unit (a reset box will cock the integrated spring before each use); 3) sterile, single-use disposable ampule that holds up to 0.3 mL of medication; 4) sterile adapter that enables the transfer of the desired medication from its vial into the disposable ampule for injection. Once the required amount of medication has been transferred into the ampule, it is attached to the injector. The injector is placed perpendicular to the injection site. The medication is released by pressing the trigger. The high velocity jet stream pierces the skin and the liquid medication disperses into the subcutaneous adipose tissue through a small orifice. Ampules, vial adapters, and needles are re-



**FIG. 1.** The needle-free system used was the Injex needle-free medication delivery system.

moved and discarded after a single use, thus eliminating the patient's injection-related risk of exposure to an infectious disease or biocontaminant.

The study drug and the placebo were loaded by a nurse who was not blinded with regard to the patient's allocation and was not involved in the biopsy procedure. Neither the patient nor the endocrinologist knew which drug had been applied. The cartridge was loaded with either 0.3 mL (6 mg) of lidocaine (Jetokain simplex ampule, Adeka Pharmaceutical Company, Istanbul, Turkey) or a similar amount of isotonic saline. The system was ready for injection in less than 5 minutes. Each patient was instructed to expect a noisy click sound and a slight stinging sensation when the injection was administered. The skin was cleaned with alcohol and was pulled taut by the operator's free hand. To provide maximum anesthesia, the injector was positioned via ultrasonographic guidance at a 90° angle on the skin overlying the thyroid nodule to be biopsied. The tip of the reservoir was pressed firmly over the site of subsequent FNAB needle insertion, and the medication or saline was injected. If the injection was properly administered, a skin impression in the shape of a tiny bull's eye remained after the removal of the injector (Fig. 2). The outer ring of the bull's eye was caused by the pressure of the cartridge edge on the skin, and the inner dot was caused by a spot of blood that marked the site of the stream of medication or saline that had been propelled through the skin. After the injection had been administered, light pressure was applied over the bull's-eye impression for several seconds with a piece of sterile cotton, and an interval of 2–3 minutes was allowed to ensure optimal anesthesia before FNAB was initiated. The bull's-eye impression at the injection site was used as a guide for the insertion of the FNAB needle. 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 (A.G.) performed all ultrasonographically guided FNABs by means of a 10-MHz linear probe (Logiq 5 Pro, GE Medical Systems, WI).

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 level of



**FIG. 2.** If the injection was properly administered, a skin impression in the shape of a tiny bull's eye remained after the removal of the injector.

discomfort during the biopsy procedure according to the following three pain rating scores:

1. A horizontal 100-mm visual analog 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 numeric 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 (12,13). In our study, satisfaction with the analgesia provided was also evaluated by reviewing each patient's response to the question of whether the local anesthetic had been satisfactory during FNAB.

#### *Statistical analysis*

All continuous data were expressed as the mean  $\pm$  SD. Data were analyzed with SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc., Chicago). 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 evaluation to determine whether there was a significant difference in pain scores between the two groups of patients. The absolute numbers according to the VRS score in each group were compared by means of the chi-square test. We determined that to achieve a 90% power of detecting a 20-mm difference on the VAS between the groups, approximately 30 patients were necessary in each treatment group. A *p* value  $<0.05$  was considered statistically significant.

#### **Results**

A total of 107 consecutive patients were allocated to receive either lidocaine ( $n=55$ ) or placebo ( $n=52$ ). The patients studied, who were assigned to one of two groups, were comparable with respect to age, sex, thyroid volume and nodule size, and nodule site (Table 1).

The results of efficacy analyses are presented in Table 2. According to the scores from all three pain scales, there was a greater statistically significant reduction in pain in the subjects

TABLE 1. PATIENT CHARACTERISTICS AND PAIN SCORES: LIDOCAINE VERSUS PLACEBO DURING THE FINE-NEEDLE ASPIRATION BIOPSY OF THYROID NODULES<sup>a</sup>

	Lidocaine (n = 55)	Placebo (n = 52)	p value
Female/male	10/45	7/45	>0.05
Age (yr)	50.3 ± 12.9	46.5 ± 12.9	>0.05
Nodule size (mean ± SD) (mm)	19.9 ± 7.9	19.2 ± 6.5	>0.05
Thyroid volume (mean ± SD) (mL)	22.6 ± 10.2	22.4 ± 11.9	>0.05
VAS (mean ± SD)	11.4 ± 13.6	38.2 ± 30.5	<0.0001
NRS (mean ± SD)	1.4 ± 1.5	3.9 ± 2.6	<0.0001
VRS (n)			
No pain	23	6	<0.0001
Mild pain	27	17	
Moderate pain	5	14	
Severe pain	0	15	

<sup>a</sup>SD, standard deviation; VAS, visual analog scale; NRS, numeric rating scale; VRS, verbal rating scale.

treated with lidocaine than in those who received placebo. The mean VAS score was 11.4 ± 13.6 in the lidocaine group and 38.2 ± 30.5 in the placebo group ( $p < 0.0001$ ). The mean NRS score of the lidocaine group (1.4 ± 1.5) was also significantly lower than that of the placebo group (3.9 ± 2.6) ( $p < 0.0001$ ). In addition, the absolute numbers according to VRS score in each group were significantly different ( $p < 0.0001$ ).

Category scales for pain intensity are presented in Table 2. The percentage of patients with no pain or mild pain in the lidocaine group was significantly higher than that in the placebo group ( $p < 0.0001$ ). Similarly, the percentage of patients with moderate-to-severe pain in the lidocaine group was significantly lower than that in the placebo ( $p < 0.0001$ ). Less than 10% of the patients in lidocaine group experienced moderate pain and none experienced severe pain.

Forty-eight patients (87.3%) in the lidocaine group (as opposed to 24 patients [46.2%] in the placebo group) reported that they were satisfied with the analgesic effect of the local anesthetic. No adverse treatment-related effects were observed.

## Discussion

FNAB is a simple, safe, cost-effective, reliable, and generally well-tolerated invasive procedure. Pain at the site of the

FNAB is not usually a serious problem when performing the FNAB using a small needle (e.g., 25-gauge). Sometimes with a larger needle (such as when draining a thyroid cyst), there may be. However, some patients complain of pain and discomfort during FNAB (1). The routine administration of any form of local anesthetic to the patient before the FNAB of a thyroid nodule is not usually recommended. Some physicians who believe that the use of an injectable anesthetic is as painful as the biopsy procedure administer no local anesthetic before FNAB is performed. Individuals with a phobia about needles and those who fear pain may find FNAB distressing or unbearable to undergo. Performing FNAB in those patients can be technically challenging for the physician. Such patients often request a nonpainful, effective, and noninvasive topical anesthetic.

The ideal method for inducing local anesthesia before a cutaneous procedure such as FNAB should be effective, fast, and portable. It should not disrupt the usual department routine or cause an additional biologic or physical risk to the patient. The needle-free system is a nearly painless rapid method of drug administration. Many clinical practices use a needle-free system of administering an analgesic agent to decrease the discomfort and pain of procedures involving routine needle punctures, such as venipuncture, intravenous catheter placement, or a digital block (3–8). The painless subcutaneous administration of insulin and human growth hormone are well-known examples of that type of technology in the field of endocrinology (3,9–11).

In a prior report, EMLA cream was successfully applied to minimize the pain associated with FNAB (2). The main disadvantage of that form of local anesthesia is that EMLA must be applied a minimum of 1 hour before FNAB to produce effective topical anesthesia, which may render its use impractical in a busy clinic. Lidocaine administered by needle-free delivery takes effect within 1–3 minutes after administration, in contrast to the 60-minute interval required by EMLA cream. That rapid onset and ease of use decrease the time associated with FNAB and enable the routine use of the needle-free delivery of lidocaine in busy clinics.

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 VAS, the NRS, and the VRS in the assessment of pain have

TABLE 2. ANALGESIC EFFICACY OF LIDOCAINE VERSUS PLACEBO DURING THE FINE-NEEDLE ASPIRATION BIOPSY OF THYROID NODULES

	Scales for pain intensity: lidocaine vs. placebo (%)							
	Lidocaine (n = 55)				Placebo (n = 52)			
	No pain	Mild pain	Moderate pain	Severe pain	No pain	Mild pain	Moderate pain	Severe pain
VAS <sup>a</sup>	49.1	49.1	1.8	0	15.4	44.2	23.1	17.3
NRS <sup>b</sup>	40.0	56.4	3.6	0	5.8	55.7	15.4	23.1
VRS <sup>c</sup>	41.8	49.1	9.1	0	11.5	32.7	26.9	28.8

<sup>a</sup>VAS, visual analog scale. 0–4 mm, no pain; 5–44 mm, mild pain; 45–74 mm, moderate pain; 75–100 mm, severe pain.

<sup>b</sup>NRS, numeric rating scale. 0, no pain; 1–4, mild pain; 5–6, moderate pain; 7–10, severe pain.

<sup>c</sup>VRS, verbal rating scale. 0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain.

been well studied, and their usefulness has been validated by several investigators (12–14).

Although the pain associated with the FNAB of thyroid nodules is well tolerated by most patients even without an anesthetic, we found that the use of lidocaine before FNAB significantly reduced the intensity of pain during that procedure and was more effective than placebo according to our patients' assessments on all three pain scales. The percentage of patients in the placebo group who experienced moderate-to-severe pain was about six times higher than that in the lidocaine group.

However, the use of lidocaine as an effective and practical topical anesthetic in patients undergoing the FNAB of a thyroid nodule may have some disadvantages. Although lidocaine application with the needle-free system significantly reduced the perceived pain intensity at the site of aspiration in many patients, most of those studied still complained about feeling mild-to-moderate pain during the FNAB. This pain appeared to be more common in patients whose FNAB was performed on a deep-seated thyroid nodule in which vigorous suction was required to obtain sufficient tissue for biopsy. We suggest that the application of lidocaine may not have penetrated to the depth required to provide complete analgesia. During the aspiration of the nodule itself, pain is almost impossible to control with any type of local anesthetic. Minimal tissue swelling underlying the biopsy site after the application of a local anesthetic, which was sometimes observed, might interfere with subsequent imaging and the targeting of an underlying nodule for FNAB, especially in those patients with a nodule size of less than 1 cm or a superficial nodule. Published studies in animal models also indicate that the pressure is not enough to puncture the media of large blood vessels (15). Thus, until additional studies in larger patient populations are conducted, it would be prudent to avoid using needle-free system in patients with a nodule positioned near a vascular structure. While our study shows that the lidocaine is effective when injected in this manner, it does not address the question of whether this "needle-free" system is superior to injection of lidocaine with a small-gauge needle. The cost of reusable jet injector is US\$325 and the total cost of the single use and disposable items including local anesthetic medication is approximately US\$5 for each patient.

Our findings indicated that this simple, needle-free, easy-to-use, disposable, lidocaine delivery system provided a rapid onset of local anesthesia before FNAB in patients with a thyroid nodule. The needle-free system differs from other available options for the administration of lidocaine, such as EMLA or subcutaneous administration with a small-gauge needle and syringe, in both onset of action and ease of administration. Most patients in this study found that a local anesthetic provided sufficient analgesia during FNAB. To our knowledge, this is the first report of the effectiveness of a needle-free system in the management of pain associated with FNAB in patients with a thyroid nodule.

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