

The Analgesic Efficacy of Lidocaine/Prilocaine Cream during Fine-needle Aspiration Biopsy of Thyroid Nodules: A Randomized Double-blind Clinical Trial

Sajjad Poursaleh, Fatemeh Safi, Hesameddin Modir¹, Malihe Safari²

Department of Radiology, School of Medicine, Arak University of Medical Sciences, ¹Department of Anesthesiology, Faculty of Medicine, Arak University of Medical Sciences, ²Department of Biostatistics, School of Medicine, Arak University of Medical Sciences, Arak, Iran

Address for correspondence: Dr. Fatemeh Safi, Department of Radiology, School of Medicine, Arak University of Medical Sciences, Arak, Iran. E-mail: safiarak@yahoo.com

ABSTRACT

Introduction: Fine-needle aspiration biopsy (FNAB) method is an effective method in diagnosis and approach to patients with thyroid nodules that create pain. This study investigates the analgesic effect of lidocaine/prilocaine cream during fine-needle aspiration (FNA) of thyroid nodules to reduce discomfort in patients during the procedure. **Materials and Methods:** In a double-blind clinical trial, two groups including patients with thyroid nodules who were rubbed with lidocaine + prilocaine 5% on their skin before FNA and patients with thyroid nodules, who have had topical placebo cream applied to their skin before FNA, were recruited. The Numerical Rating Scale was used to check the pain level. The Chi-square test, Fisher's exact test, independent *t*-test, and Mann-Whitney's nonparametric test were used for data analysis in SPSS software. **Results:** The average pain sensation in the intervention group is lower than the scores obtained in the control group, but despite the existing difference, this difference was not statistically significant ($P = 0.7$). The investigations showed that with the increase in the size and diameter of the thyroid nodules, the amount of pain that the patient feels during the procedure is reduced. Moreover, increasing the size of the nodule significantly reduces the amount of pain felt by the patient in the intervention group ($P = 0.04$). **Conclusion:** The results of this study indicated that the use of lidocaine/prilocaine cream in patients who are candidates for thyroid nodule biopsy did not have a significant effect on reducing their pain in contrast with literature. Therefore, based on the findings of the study, the use of lidocaine/prilocaine cream in these patients does not offer any significant decrease in pain sensation compared to using just a placebo.

Key words: Aspiration, lidocaine, pain, prilocaine, thyroid nodule

INTRODUCTION

There are several methods to obtain tissue samples from thyroid nodules. An effective method in diagnosing and approaching patients with thyroid nodules is the fine-needle aspiration biopsy (FNAB) method.^[1] Fine-needle aspiration (FNA) is a sampling method in which a needle is used instead of surgical incision and tissue removal.^[2] In this method, a thin needle is inserted into the desired tissue or liquid, and with its help, the sample is removed from the tissue or liquid.^[3] FNAB is a very accurate cytological technique in differentiating between benign and malignant disease.^[4] This method is short-term and can easily be applied to outpatients to determine tissue cytology.^[5] Therefore, it has become one of the most common, reliable, and affordable diagnostic methods.^[6] Similarly, thyroid FNAB is very reliable as the gold-standard method in the differential

diagnosis of thyroid nodules.^[7] Most thyroid nodules are benign, however, 5%–15% of them are malignant.^[8] For many thyroid nodules, fine-needle sampling is the most important step in the accurate diagnosis of the disease and its treatment.^[9] In the past and before the FNA method was available, in some cases, the doctor had to remove a large amount of the thyroid gland during the operation to make sure that the patient was not at risk of malignancy.^[10] This method, sometimes, requires the patient to take medicine or face side effects after that.^[11] However, with the use of current advanced methods, patients no longer struggle with past issues and do not need anesthesia and surgery for biopsy and sampling.^[12] In this type of biopsy, which is performed

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Access this article online

Quick Response Code:



Website:
www.jhnps.org

DOI:
10.4103/jhnps.jhnps_28_24

How to cite this article: Poursaleh S, Safi F, Modir H, Safari M. The analgesic efficacy of lidocaine/prilocaine cream during fine-needle aspiration biopsy of thyroid nodules: A randomized double-blind clinical trial. *J Head Neck Physicians Surg* 2024;12:44-9.

Submitted: 06-Feb-2024 **Revised:** 30-Mar-2024 **Accepted:** 25-Apr-2024

Published: 14-Jun-2024

in a minimally invasive way, a narrow needle is used for biopsy.^[13-15] The pain caused by this biopsy does not require general anesthesia, but it can cause discomfort in the patient pain caused by biopsy, especially when the needle enters the skin, can cause stress and anxiety in the patient.^[16] Although this procedure is performed in a short period of time, some patients complain of excruciating pain during FNAB.^[4,17] Although most of the time this procedure is associated with little discomfort for the patients, it is possible to reduce the discomfort during the procedure by reducing the pain during the biopsy through the use of local anesthetics.^[18,19] However, a standard method to reduce the discomfort of patients during FNAB has not been stated in the existing references, and generally, this procedure is performed without anesthesia methods.^[20] This study investigated the analgesic effect of lidocaine/prilocaine cream during FNA of thyroid nodules to reduce discomfort in patients during the procedure.

MATERIALS AND METHODS

This study was conducted in the form of a double-blind, placebo-controlled clinical trial in patients referred to the Outpatient Ultrasound Clinic of Arak Hospitals. This study aimed to evaluate the analgesic effect of lidocaine/prilocaine cream during FNA of thyroid nodules to reduce discomfort in patients during the procedure. Therefore, 160 eligible patients visited the outpatient clinics of Arak hospitals for the first time to perform FNA of thyroid nodules. The minimum required sample size was estimated using the following formula and considering type I error (alpha) 0.05, power (1-beta) 0.90, effect size 0.81, and two-way alternative hypothesis (H1), 79 patients in each group. The samples were selected as permutation blocks from patients with thyroid nodules who were referred to the thyroid clinic of Arak Hospitals for FNA.

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

$Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$, $\mu_1 = 2.61$, $\mu_2 = 1.31$, $SD_1 = 1.91$, $SD_2 = 1.69$.

In this study, patients were examined who were already under ultrasound and the presence of thyroid nodules was confirmed in them. Patients with nodules larger than 1 cm were examined. Patients with altered mental status or inability to understand the questions, a history of long-term use of opioids or analgesics, or an allergy to the drug used in the study will be excluded. Therefore, inclusion criteria included people with a minimum age of 18 years and a maximum age of 70 years and patients

with a thyroid nodule over 1 cm in ultrasound. Exclusion criteria: (1) lack of consent for cooperation, (2) taking psychiatric medication, (3) patients with altered mental status or inability to understand questions, (4) history of long-term use of opioids or painkillers, and (5) allergy to the drugs.

This study was a double-blind clinical trial study in such a way that the colleagues in charge of pain investigation and the statistical analyst did not know the type of grouping of the research units. The study groups include two groups: (1) patients with thyroid nodules who were rubbed with lidocaine + prilocaine 5% local anesthetic cream of Tehran Chemical Pharmaceuticals on their skin before FNA and (2) patients with thyroid nodules, who have had topical placebo cream applied to their skin before FNA. For patient allocation to study arms, an identification number was assigned by a computer-based system to the patients and they were assigned to each group by block randomization method as shown in Figure 1. Block size considered 4.

The creams were applied to the biopsy site in a certain and equal amount by a nurse who did not know the type of cream. Placebo cream consists of a white lotion similar to lidocaine/prilocaine cream. Lidocaine + prilocaine 5% local anesthetic cream of Tehran Chemie Pharmaceuticals in an amount of 2.5 mL (~2.5 g) similar to the amount of placebo cream was used uniformly in a thick layer on the biopsy site of the nodule 60 min before the procedure. The person who performs the procedure does not know the contents of the cream used. Sampling was done by needle number 25 for each patient. The same ultrasound probe will be used for all patients' thyroid nodules and patients were classified based on the standard classification for the modified TI-RADS system.^[21] After the procedure, the patients were immediately transferred to another room and were checked by the researcher in terms of their pain scores during FNA.

The Numerical Rating Scale (NRS) was used to check the pain level. In this way, a person rates his pain using a scale of 0–10. Zero means no pain and 10 means the worst pain condition. Demographic information, including age and sex, as well as the diameter of the nodule and the number of needles inserted into the skin for sampling, were recorded by the researcher.

Statistical analysis

After completing the data information, it was entered into statistical software. Descriptive statistics were expressed for quantitative variables with mean and standard deviation, and for qualitative variables with frequency and percentage. Then, to compare the quantitative characteristics of the

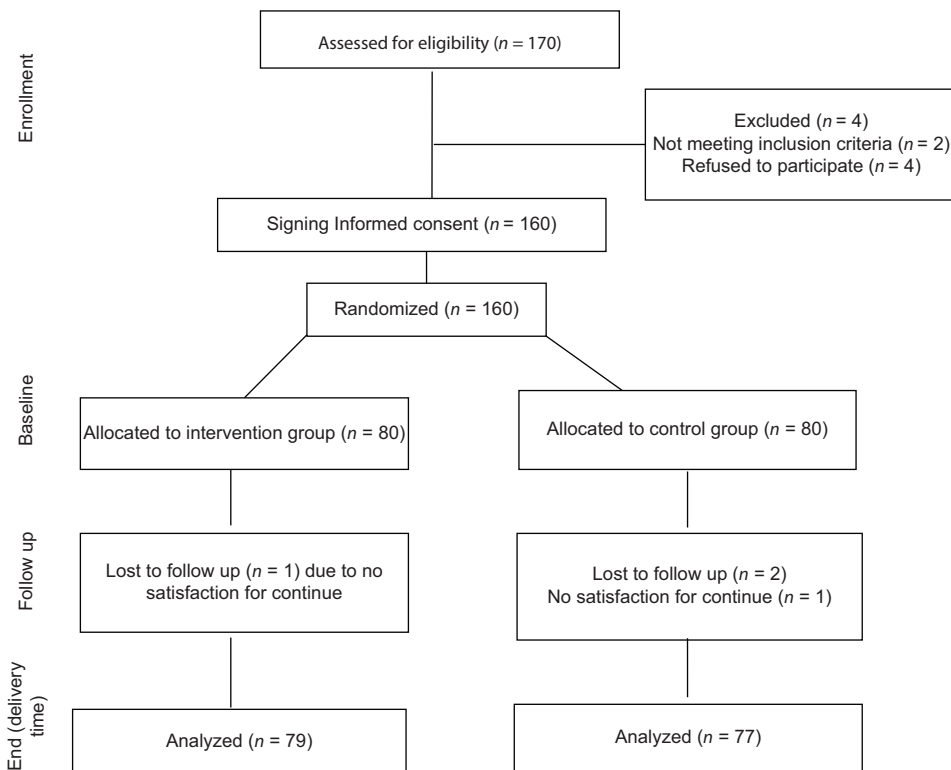


Figure 1: CONSORT diagram showing the flow of participants through each stage of a randomized trial

two groups, the Student's *t*-test of two independent groups was used, and the Chi-square test was used to compare the qualitative characteristics. Correlation analysis was also used to determine the relationship between quantitative variables. SPSS 24.0 (IBM Corp., Armonk, NY) software was used for data analysis at a significance level of 5%.

Ethical aspects

The study was approved by the Research Committee in Ethics of Arak University of Medical Sciences, vide letter no IR.ARAKMU.REC.1401.310 on September 1, 2023, and the clinical registry number IRCT20221212056796N1 on April 15, 2023.

Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures in the study follow the guidelines laid down in the Declaration of Helsinki (2013).

RESULTS

In terms of age frequency, the average age of the participants in this study was 48.31 in group A and 48.01 in group B. There was no statistically significant difference between the two groups in terms of age. The youngest person was 20 and the oldest person was 70 years old. Furthermore, in terms of gender, there were 71 women and 9 men in group A, and 76 women and 4 men in group B. There was

no significant difference between the two intervention and control groups in terms of gender. As shown in Table 1, the mean NRS scores were compared between the two groups. Statistical analyses showed that the average pain sensation in the intervention group was lower than the scores obtained in the intervention group, but despite the existing difference, this difference was not statistically significant ($P = 0.7$).

The relationship between the amount of pain in people and the size of the thyroid nodule in both groups was investigated and compared. The investigations showed that with the increase in the size and diameter of the thyroid nodules, the amount of pain that the patient feels during the procedure is reduced. Furthermore, the data and statistical analysis showed that in the intervention group, increasing the size of the nodule significantly reduced the amount of pain felt by the patient ($P = 0.04$). This relationship was not significant in the intervention group ($P = 0.2$) [Table 2].

In this study, the relationship between the amount of pain felt by the patient and the number of times the needle was inserted into the skin was compared. The investigations showed that the average score of NRS increases with the increase in the number of times the needle enters the skin in both groups, and with the increase in the number of times the needle enters the skin, the patients feel more pain. Despite the clear changes in the NRS score in both groups following the increase in the number of needle insertions,

these changes were not statistically significant ($P > 0.05$). The results are shown in Table 3.

In addition, in this study, people were analyzed in terms of the relationship between age and the amount of pain felt during the procedure. The investigations showed that increasing age has no effect on the amount of pain felt, and no significant relationship was found between age and NRS score in patients ($P = 0.2$). The results are shown in Table 4. In addition, in this study, the relationship between the gender of the subjects and the amount of pain felt by the patient during the procedure was evaluated. As shown in Table 5, the male group reported significantly ($P = 0.01$) lower levels of pain than the female group. Although in the control group, the male group reported lower NRS scores

than the female group, this difference was not statistically significant.

DISCUSSION

In this study, the average age of people and its relationship with the level of pain in two groups were investigated. The average age of the participants in this study was 48.31 in the intervention group and 48.01 in the intervention group. The standard classification for the modified TI-RADS system^[21] showed that a significant difference was found between the pain severity in group A, grade 1 (3 months after the injection) and grade 3 (6 months after the injection), and the previous follow-up. In group B, only patients with grade 1 had lower pain severity 6 months after the injection.

The severity of disability exhibited a significant difference between group A, grade 1 (3 months after the injection), grade 2 (6 months after the injection), and grade 3 (2 weeks after the injection), and the previous follow-up. In group B, patients with grade 1 had disability improvement 3 months after the injection, and patients with grade 3 had improvement 2 weeks after the injection. Regardless of the canal stenosis grade, the severity of disability decreased in group A after 2 weeks. Gursoy *et al.*^[22] conducted a study on 50 women with nodular goiter who were candidates for FNA, and they were examined in two groups of 25 in terms of pain sensation after the procedure with and without the use of lidocaine cream. The average age of the studied subjects in their two groups was 47.45 and 50.71. In this study, it was proven that the average age of people has no significant relationship with the level of pain, and the results of this study confirmed the previous results. Furthermore, in this study, people were examined in terms of the relationship between gender and pain level after sampling. About 90% of the participants in this study were women. The present study proved that higher degrees of pain after the procedure were reported in females. Demirci *et al.*,^[20] in a study conducted on 109 patients who underwent thyroid nodule biopsy, showed that women reported higher degrees of pain during the procedure. The above items were statistically significant in that study. In this study, statistical analysis showed a significant relationship between female gender and feeling of pain after the procedure. Contradictory results have been obtained in various studies regarding the amount of pain after thyroid nodule biopsy. In a study conducted by Liao *et al.*^[23] on 183 patients with thyroid nodules who underwent thyroid nodule biopsy with and without local anesthesia, in the results, 92% of people with local anesthesia and 80% of subjects without local anesthesia reported mild or no pain; the results were significant. The results of this study, along with the results of Gursoy's study,^[22] show that there is no

Table 1: Average scores obtained from the Numerical Rating Scale in two control and intervention groups

	Control	Intervention	P
NRS score, mean±SD	4.53±2.64	4.24±2.68	0.70
NRS: Numerical Rating Scale, SD: Standard deviation			

Table 2: Correlation of pain level and thyroid nodule diameter in two groups

Groups	Control, <i>r</i> (<i>P</i>)	Intervention, <i>r</i> (<i>P</i>)
Pain level	-0.13 (0.26)	-0.022 (0.04)

Table 3: Investigating the relationship between the number of times the needle is inserted into the skin and the level of pain felt by the patient

Needle insertion times	Control	Intervention	P
1	3.75±2.5	3±2.83	0.425
2	4.27±2.47	4.15±2.55	0.423
3	4.24±2.86	4.33±2.88	0.689
4	5.25±3.59	7±1.73	0.065

Table 4: Correlation of pain level with age separately between control and intervention groups

Groups	Control, <i>r</i> (<i>P</i>)	Intervention, <i>r</i> (<i>P</i>)
Pain level correlation with age	0.04 (0.70)	0.13 (0.20)

Table 5: Examining the relationship between gender and average Numerical Rating Scale scores in two control and intervention groups

Group	Gender	Mean±SD	P
Control	Women	4.07±2.72	0.11
	Men	3.11±1.36	
Intervention	Women	4.38±2.66	0.01
	Men	1.5±1.00	

SD: Standard deviation

significant relationship between the use of lidocaine cream and the reduction of pain in patients after biopsy. The results of this study showed that increasing the number of times the needle is inserted for sampling does not have a significant effect on the patient's feeling of pain.

CONCLUSION

In general, the results of the present study do not support the results of most of the studies conducted on the routine use of lidocaine cream in patients who are candidates for thyroid nodule biopsy. The results of this study indicated that the use of lidocaine/prilocaine cream in patients who are candidates for thyroid nodule biopsy did not have a significant effect on reducing their pain, and based on the findings of the study, the use of lidocaine/prilocaine cream in these patients does not offer any significant decrease in pain sensation compared to using just placebo.

Acknowledgments

We would like to thank all the radiology attending professors, medical residents, and nursing staff for data collection and their meticulous patient care. Moreover, we are grateful to Arak University of Medical Sciences for financial support of this work.

Author contributions

SP and FS worked on concepts and study design, manuscript editing, and manuscript review. HM and MS worked on the definition of intellectual, content literature search, clinical studies, data acquisition statistical data analysis, as well as manuscript editing and manuscript review. All authors reviewed the final draft and approved it.

Financial support and sponsorship

This study was funded by the Arak University of Medical Sciences.

Conflict of interest

There are no conflicts of interest.

Disclosure

This material has never been published and is not currently under evaluation in any other peer-reviewed publication.

Ethical approval

The permission was taken from the Institutional Ethics Committee before starting the project. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the

1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

REFERENCES

- Alexander EK, Heering JP, Benson CB, Frates MC, Doubilet PM, Cibas ES, *et al.* Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. *J Clin Endocrinol Metab* 2002;87:4924-7.
- Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, *et al.* American Association of Clinical endocrinologists and associazione medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract* 2006;12:63-102.
- Eidelman A, Weiss JM, Lau J, Carr DB. Topical anesthetics for dermal instrumentation: A systematic review of randomized, controlled trials. *Ann Emerg Med* 2005;46:343-51.
- Flynn A, Barry R. Use of ethyl chloride in dermatology minor surgery. *Dermatol Surg* 2016;42:433-4.
- Heller GZ, Manuguerra M, Chow R. How to analyze the visual analogue scale: Myths, truths and clinical relevance. *Scand J Pain* 2016;13:67-75.
- Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, *et al.* American Association of Clinical endocrinologists, American College of endocrinology, and Associazione Medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules – 2016 Update. *Endocr Pract* 2016;22:622-39.
- Raber M, Scattoni V, Roscigno M, Rigatti P, Montorsi F. Perianal and intrarectal anaesthesia for transrectal biopsy of the prostate: A prospective randomized study comparing lidocaine-prilocaine cream and placebo. *BJU Int* 2005;96:1264-7.
- Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: A reanalysis of two clinical trials of postoperative pain. *J Pain* 2003;4:407-14.
- Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain* 2000;16:22-8.
- Kang HW, No JH, Chung JH, Min YK, Lee MS, Lee MK, *et al.* Prevalence, clinical and ultrasonographic characteristics of thyroid incidentalomas. *Thyroid* 2004;14:29-33.
- Ylagan LR, Farkas T, Dehner LP. Fine needle aspiration of the thyroid: A cytohistologic correlation and study of discrepant cases. *Thyroid* 2004;14:35-41.
- Nam-Goong IS, Kim HY, Gong G, Lee HK, Hong SJ, Kim WB, *et al.* Ultrasonography-guided fine-needle aspiration of thyroid incidentaloma: Correlation with pathological findings. *Clin Endocrinol (Oxf)* 2004;60:21-8.
- Lee TL, Wei PY, Tai SK. Effect of local anesthesia on pain scale and specimen adequacy in fine-needle aspiration biopsy of thyroid nodules for liquid-based cytology. *Sci Rep* 2022;12:18498.
- Pantanowitz L, Thompson LD, Jing X, Rossi ED. Is thyroid core needle biopsy a valid compliment to fine-needle aspiration? *J Am Soc Cytopathol* 2020;9:383-8.
- Rodrigues MG, da Silva LF, Araujo-Filho VJ, Mosca LM, Araujo-Neto VJ, Kowalski LP, *et al.* Incidental thyroid carcinoma: Correlation between FNAB cytology and pathological examination in 1093 cases. *Clinics (Sao Paulo)* 2022;77:100022.
- Lander J, Nazarali S, Hodgins M, Friesen E, McTavish J, Ouellette J, *et al.* Evaluation of a new topical anesthetic agent: A pilot study. *Nurs Res* 1996;45:50-3.
- Speirs AF, Taylor KH, Joanes DN, Girdler NM. A randomised, double-blind, placebo-controlled, comparative study of topical skin

- analgesics and the anxiety and discomfort associated with venous cannulation. *Br Dent J* 2001;190:444-9.
18. Irkoren S, Ozkan HS, Karaca H. A clinical comparison of EMLA cream and ethyl chloride spray application for pain relief of forehead botulinum toxin injection. *Ann Plast Surg* 2015;75:272-4.
 19. Moon YE, Kim SH. Effects of ethyl chloride spray on pain and parameters of needle electromyography in the upper extremity. *Am J Phys Med Rehabil* 2014;93:869-75.
 20. Demirci H, Erdamar H, Karakoc A, Arslan M. Thyroid fine needle aspiration biopsy: Is topical local anaesthesia beneficial? *Int J Clin Pract* 2010;64:25-8.
 21. Li M, Wei L, Li F, Kan Y, Liang X, Zhang H, *et al.* High risk thyroid nodule discrimination and management by modified TI-RADS. *Cancer Manag Res* 2021;13:225-34.
 22. Gursoy A, Ertugrul DT, Sahin M, Tutuncu NB, Demirel AN, Demirag NG. Needle-free delivery of lidocaine for reducing the pain associated with the fine-needle aspiration biopsy of thyroid nodules: Time-saving and efficacious procedure. *Thyroid* 2007;17:317-21.
 23. Liao LJ, Lo WC, Hsu WL, Cheng PW, Wang CP. Assessment of pain score and specimen adequacy for ultrasound-guided fine-needle aspiration biopsy of thyroid nodules. *J Pain Res* 2018;11:61-6.