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Topical lidocaine anesthesia for nasopharyngeal sampling – a double-blind randomized placebo-controlled trial

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ABSTRACT

Introduction and aim. The aim of this study is to evaluate the effects of topical lidocaine application for nasopharyngeal sampling, on pain perception, the comfort of the patients, and the application difficulty for healthcare staff.

Material and methods. This study conducted with 100 healthy volunteers (50 participants in Lidocaine group and 50 participants in Placebo group). Two ml of a solution containing 10 mg/ml of lidocaine was applied to each nostril of the participants in the Lidocaine group, and the same dose of 0.9% NaCl to the Placebo group. We compared the changes in pain intensity and discomfort intensity using two numerical rating scales, the frequency of undesirable reactions, and the judgment of the practitioner staff.

Results. There were statistically significant decreases in pain and discomfort scores in the Lidocaine group. Similarly, there were statistically significant decreases in the frequency of all undesirable reactions except “grimace”, in the second sampling in the Lidocaine group, however, there was a statistically significant decrease only in “holding staff’s hand” in second sampling in the Placebo group.

Conclusion. Intranasal lidocaine application reduces the pain that occurs during nasopharyngeal sampling and makes the procedure easier for the patient and the healthcare worker.

Keywords. COVID-19 testing, lidocain, nasopharynx, swab

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has had different effects on emergency service.¹⁻³ Emergency medicine staff take part in the diagnosis and treatment of COVID-19.⁴⁻⁶ Performing nasal or nasopharyngeal sampling for the polymerase chain reaction (PCR) test in suspected cases presenting to the emergency department is one of the tasks performed by the emergency department staff within this period.^{4,5}

Nasopharyngeal sampling is used in the diagnosis of many respiratory diseases. It is also used for the

polymerase chain reaction (PCR) test, which is accepted as the current standard procedure of case detection in the COVID-19 pandemic.^{7,8} Failure to use an appropriate technique in this diagnostic method for COVID-19 cases may cause false-negative results.⁹ Although it is a generally safe diagnostic method, the application of this test, which is performed millions of times a day globally due to the pandemic, without using the correct technique can cause a serious number of complications.¹⁰

McElfish et al. aimed to investigate the perceived barriers to COVID-19 testing, and they reported that the

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people's perception of the nasal swab method is irritating and too painful is one of the primary barriers to testing.¹¹ The general opinion of participants is that this test is painful and uncomfortable, a more "patient-friendly" method can convince more people to take the test, and researchers should find a "new test method" for this purpose.¹¹ If there is no chance of contactless sampling, the staff being at a distance of less than 2 meters to the case creates a low risk of contamination even if they have sufficient personal protective equipment.¹² The less pain and more compliant the patient is; the easier nasal swab will be applied. This may also reduce the risk of case-to-healthcare worker transmission, because of reducing the potential aerosol-generating characteristic of nasopharyngeal sampling.¹³ Lidocaine has been used for local anesthesia of the nasopharynx, and has been found to be effective and safe in different studies for different purposes, but, to the best of our knowledge, not nasopharyngeal swab sampling.^{14,15} However, Kanodia et al. studied to evaluate the effects of topical lignocaine application on the patient's comfort in oropharyngeal swab sampling for COVID-19.¹⁶

Aim

Our study aimed to evaluate the effects of topical lidocaine application for nasopharyngeal sampling, on pain perception, the comfort of the individuals, and the application difficulty for healthcare staff.

Material and methods

Study design and setting

This study is a prospective randomized placebo-controlled study with restricted randomization of an allocation ratio of 1:1. We used Random Allocation Software (RAS) for randomization.¹⁷ The study was conducted following the CONSORT guideline and the tenets of the Declaration of Helsinki at our Emergency Department between 01.09.2020 and 30.09.2020 after obtaining the approval of the Clinical Research Ethics Committee.¹⁸ We have been registered in a clinical trial database (ClinicalTrials.gov Identifier: NCT04885777). Also, the written informed consent of all participants was obtained.

The study population consisted of 100 healthy volunteers, 50 individuals in the Lidocaine group, and 50 individuals in the Placebo group. Initially, we evaluated all participants for eligibility by the inclusion and exclusion criteria. The inclusion criteria of the study were: (1) being 18 years and older, and (2) volunteering to participate in the study. The exclusion criteria of the study were: (1) taking analgesic drugs before admission, (2) pregnancy, (3) lactation, (4) having a bleeding disorder, (5) known allergy to Lidocaine, (6) previous nasal trauma or operation, (7) having respiratory tract infection symptoms (such as fever, headache, runny nose, sore throat, cough, sneeze, breathlessness), and (8) having a

chronic disease (diabetes, cancer, heart disease, asthma, COPD, etc.).

Allocation to the study arms was performed using sealed and opaque envelopes to ensure allocation concealment. The participants were allocated using the random allocation sequence list which we generated via RAS software.

Measurements

The sample collection procedure was categorized into four steps, which were; (1) inserting the swab in the nostril, (2) hitting the back of the nasopharyngeal cavity, (3) rotating five times, and (4) removing slowly. To evaluate the placebo effect, we performed two-stage sampling procedure. Initially, a naso pharyngeal swab was performed on each group without any intervention. We waited at least one hour for the second sample collection. If the participant was still in pain or felt discomfort due to the first sampling, the waiting time has been extended. At this stage, one ml of a solution containing 20 mg/ml of lidocaine (Aritmal %2, OSEL İlaç San. ve Tic. A.Ş., Turkey), was applied to each nostril of the participants in the Lidocaine group. Thus, a total of 40 mg of lidocaine, 20 mg for each nostril, was given to the individuals of the Lidocaine group. The Placebo group received only a total of 2 ml of 0.9% NaCl (one ml for each nostril). The second samples were collected after waiting 5 minutes following the administration of the solution. All participants were instructed not to eat or drink for 30 minutes following the sampling procedure to avoid the risk of aspiration. All these procedures were performed by two emergency medicine physicians. We did not send the samples to any laboratory test. All used swabs were disposed of in a medical waste box following the healthcare waste-management policy of our hospital.

To provide double-blinding, all solutions (both with and without Lidocaine) were previously prepared in coated 5 ml syringes without needle (BD Biosciences, USA), and numbered these syringes consecutively by an independent physician. Participants and performer physicians did not know the group number represents which solution until inputting the study data.

Age (year) and sex of the participants were recorded. There are four primary outcomes of the study. The first and second are the changes in the severity of pain and discomfort that were felt during the sampling procedure. These outcomes were measured via a paper questionnaire that had two Numerical Rating Scale (NRS) which the first one is for pain intensity and the second one is for discomfort intensity. The NRSs were 100 mm scales ranging from 0 to 10 (0 as the absence of pain/discomfort and 10 as unbearable pain/discomfort). We gave the questionnaire to the participants and explained how to perform. The scores were recorded two times by the participants after the first and second sampling processes.

The third primary outcome is the frequency of undesirable reactions during sample collection. We recorded head retraction, holding practitioner staff's hand, grimace, cough, and sneeze as the undesirable reaction during the sampling procedure.

The fourth primary outcome is the judgment of the practitioner staff about the sampling procedure. We included the appropriateness and the difficulty of the sample collection procedure, for this outcome. If four steps of the sampling procedure (inserting in the nostril, hitting the back of the nasopharyngeal cavity, rotating five times, and removing) have been completed successfully, practitioner staff defined the sampling as appropriate. If one or more of these steps has not been completed, the staff retried one more time. If still there has been a problem in these steps, the staff defined the procedure as inappropriate. The practitioner staff performed a five-point Likert scale (1-minimally difficult, 2-slightly difficult, 3-moderately difficult, 4-substantially difficult, 5-extremely difficult) for measuring the difficulty of the procedure.

Statistical analysis

We calculated the minimum required sample size using G Power 3.1 software as 41 individuals in each study group (totally of 82 participants with an allocation ra-

tio of 1:1), with a medium effect size of 0.5, type 1 error of 0.05, and a power of 0.80 for Mann-Whitney U Test¹⁹. Also, we calculated the sample size as 31 individuals (for each group) with the same parameters for Wilcoxon Signed Rank Test. After then, we performed one more calculation for McNemar Test with an Odds ratio of 3, type 1 error of 0.05, a power of 0.80, and a total proportion of expected discordant pairs, and we found the minimum required sample size as 39 for this test. Finally, we approved the minimum required sample size for the study was 82 (41 people in each group).

Statistical analyses were conducted using the SPSS version 20 statistical software (IBM Corp. in Armonk, NY). Descriptive data are presented as mean with standard deviation and median with interquartile range for numerical variables, and the frequency with percentage for categorical variables. Shapiro-Wilk and Kolmogorov – Smirnov tests were used to evaluate the distribution of the numeric data. Independent-Samples Mann–Whitney U test was used for comparing non-normally distributed numeric and ordinal data between Lidocaine and Placebo groups. Related-Samples Wilcoxon Signed Rank Test was used for comparing non-normally distributed numeric and ordinal data among first and second samplings. Pearson chi-square and Fisher's Exact Test were used for comparing categorical variables be-

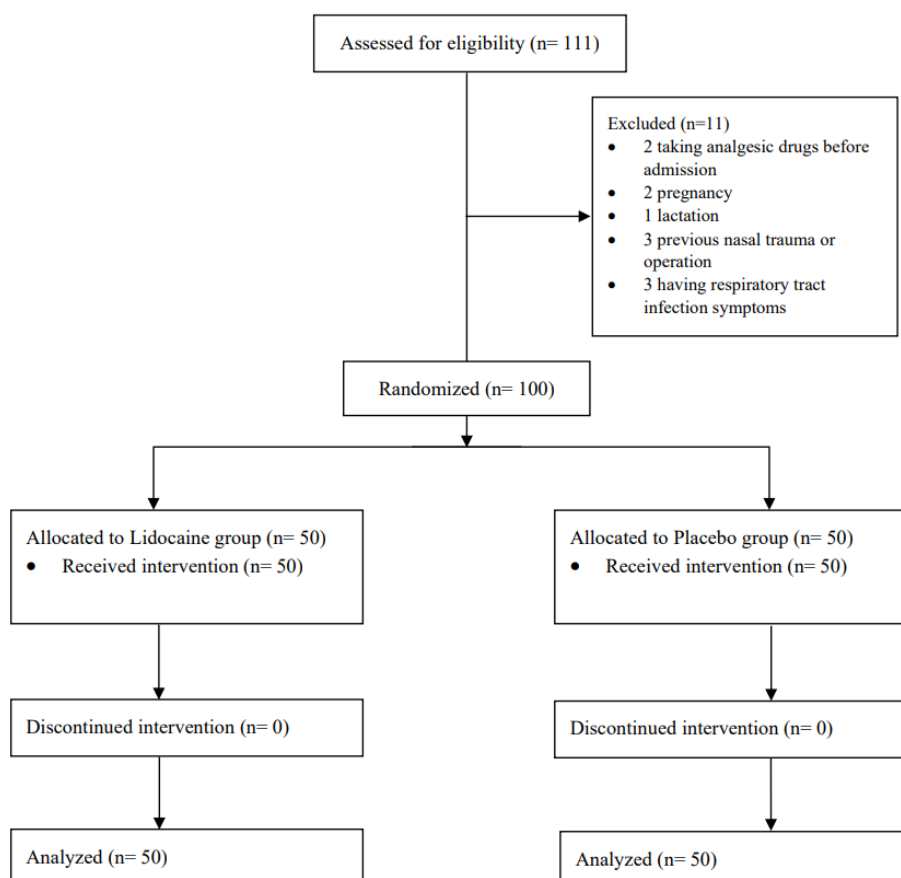


Fig. 1. CONSORT flow diagram of study

tween two study groups. Related-Samples McNemar Test was used for comparing categorical variables between first and second samplings. $p < 0.05$ was considered as the statistically significant level.

Results

This study was conducted with healthy volunteers. We assessed the participants for eligibility according to the inclusion and exclusion criteria. After excluding 11 individuals, 100 people were randomized into two study arms half and half. There was no lost to follow-up, and we analyzed all 100 participants' data (Fig. 1).

The mean age of participants was 34.5 ± 9.8 years and 35.4 ± 8.9 years, and the males were 30.0% and 33.0% in Lidocaine and Placebo groups, respectively (Table 1).

Table 1. Demographics of the patients

Demographics	Lidocaine group (n= 50)	Placebo group (n= 50)
Age (years)		
Mean \pm SD	34.5 \pm 9.8	35.4 \pm 8.9
Median (IQR)	32.0 (26.0-42.3)	36.0 (27.8-40.3)
Sex (male), n (%)	30 (60.0)	33 (66.0)

SD – standard deviation, IQR – interquartile range

In the first sampling process, pain and discomfort scores were statistically similar in both Lidocaine and Placebo groups. In the second sampling, there were statistically significant decreases in pain and discomfort scores when compared to the first sampling procedures in the Lidocaine group ($p < 0.001$ and $p < 0.001$, respectively). However, pain and discomfort scores were statistically similar among first and second samplings in the Placebo group (Table 2).

The frequencies of all undesirable reactions were statistically similar among the Lidocaine group and the Placebo group in the first sample collection. There were statistically significant decreases in the frequency of head retraction, holding staff's hand, coughing, and sneezing in second sampling when compared to first sampling in the Lidocaine group (< 0.001 , < 0.001 , < 0.001 , and < 0.001 , respectively). However, there was a statistically significant decrease only in holding staff's hand in second sampling in the Placebo group ($p = 0.004$). On the other hand, there was no statistically significant difference in grimace between first and second sampling processes both in Lidocaine and Placebo groups (Table 3).

Table 4 presents health staff's judgments on sampling procedure. The appropriateness rate of the first sampling process was statistically similar according to

Table 2. Comparison of pain and discomfort scores

Variables		Placebo group (n= 50)	Lidocaine group (n= 50)	p^*
Pain score in first sampling	Mean \pm SD	6.3 \pm 2.2	6.1 \pm 2.0	0.756
	Median (IQR)	6.0 (5.0-8.0)	6.5 (5.0-8.0)	
Pain score in second sampling	Mean \pm SD	5.9 \pm 2.2	1.9 \pm 1.7	-
	Median (IQR)	6.0 (4.0-8.0)	2.0 (1.0-2.0)	
	p^{**}	0.309	< 0.001	
Discomfort score in first sampling	Mean \pm SD	7.0 \pm 2.3	7.1 \pm 1.9	0.813
	Median (IQR)	7.0 (5.0-9.0)	7.0 (6.0-8.3)	
Discomfort score in second sampling	Mean \pm SD	6.7 \pm 2.2	2.0 \pm 1.8	-
	Median (IQR)	7.0 (5.0-9.0)	2.0 (0.0-3.0)	
	p^{**}	0.226	< 0.001	

SD – standard deviation, IQR – interquartile range, * independent-samples Mann-Whitney U test was used, ** related-samples Wilcoxon signed rank test was used

Table 3. Comparison of patient reactions

Variables	Placebo group (n= 50)	Lidocaine group (n= 50)	p
Head retraction in first sampling, n (%)	36 (72.0)	32 (64.0)	0.391*
Head retraction in second sampling, n (%)	36 (72.0)	5 (10.0)	-
p^{**}	> 0.999	< 0.001	
Holding staff's hand in first sampling, n (%)	20 (40.0)	14 (28.0)	0.205*
Holding staff's hand in second sampling, n (%)	8 (16.0)	0 (0.0)	-
p^{**}	0.004	< 0.001	
Grimace in first sampling, n (%)	47 (94.0)	46 (92.0)	$> 0.999^{***}$
Grimace in second sampling, n (%)	48 (96.0)	44 (88.0)	-
p^{**}	> 0.999	0.754	
Cough in first sampling, n (%)	18 (36.0)	25 (50.0)	0.157*
Cough in second sampling, n (%)	13 (26.0)	4 (8.0)	-
p^{**}	0.063	< 0.001	
Sneeze in first sampling, n (%)	12 (24.0)	14 (28.0)	0.648*
Sneeze in second sampling, n (%)	18 (36.0)	0 (0.0)	-
p^{**}	0.238	< 0.001	

* Pearson chi-square test was used, **related-samples McNemar test was used, *** Fisher's exact test was used

health staff among the two study groups. Also, there was no statistically significant difference in the appropriateness between the first and the second samplings both in Placebo and Lidocaine groups.

Table 4. Comparison of staff's judgments

Variables	Placebo group (n= 50)	Lidocaine group (n= 50)	p
Appropriateness of first sampling, n (%)	46 (92.0)	45 (90.0)	>0.999*
Appropriateness of second sampling, n (%)	48 (96.0)	49 (98.0)	-
<i>p</i> **	0.625	0.219	
Difficulty of first sampling, n (%)			0.649***
Minimal	9 (18.0)	7 (14.0)	
Slight	8 (16.0)	11 (22.0)	
Moderate	16 (32.0)	19 (38.0)	
Substantial	10 (20.0)	8 (16.0)	
Extreme	7 (14.0)	5 (10.0)	
Difficulty of second sampling, n (%)			-
Minimal	3 (6.0)	26 (52.0)	
Slight	14 (28.0)	15 (30.0)	
Moderate	15 (30.0)	6 (12.0)	
Substantial	13 (26.0)	3 (6.0)	
Extreme	5 (10.0)	0 (0.0)	
<i>p</i> ****	0.589	<0.001	

* Pearson chi-square test was used, **related-samples McNemar test was used, *** independent-samples Mann-Whitney U test was used, **** related-samples Wilcoxon signed rank test was used

The difficulty of first sample collection was statistically similar among Placebo and Lidocaine groups according to staff opinion. However, practitioner staff expressed that the second sampling process was easier than the first sampling in the Lidocaine group. This difference was statistically significant (<0.001). Besides this, staff found the difficulty of first and second sampling procedures similar in the Placebo group (Table 4).

Discussion

Although we found that the pain and discomfort scores were similar among the two study groups before the intervention, there were statistically significant decrease in pain and discomfort scores only in the Lidocaine group after intervention. Similarly, there were statistically significant decreases in the frequency of all undesirable reactions except grimace, in the second sampling in the Lidocaine group, however, there was a statistically significant decrease only in holding staff's hand in second sampling in the Placebo group. The practitioner staff expressed that the second sampling was easier than the first in the Lidocaine group, but the difficulties of the first and second sampling processes were similar in the

Placebo group. Besides, they decided that the appropriateness of the first and second procedures were similar both in the Lidocaine group and Placebo group.

Among the important control approaches to combating the COVID-19 pandemic is increasing the number of tests to detect as many cases as possible.²⁰ In COVID-19 diagnostic testing, upper respiratory tract (URT) samples such as nasal, nasopharyngeal, and oropharyngeal samples are recommended at the first stage. However, it is recommended to take lower respiratory tract samples in patients with negative results in URT samples and still clinically suspected COVID-19.²¹ Nasal (middle turbinate), oropharyngeal, and nasopharyngeal sample collection are acceptable alternative methods for PCR, although nasopharyngeal sample collection is generally recommended by the Center for Disease Prevention and Control and the World Health Organization.^{21,22} The nasopharyngeal swab is a widely used specimen worldwide, because of its high-grade sensitivity.²³ However, due to the difficulties in application, methods based on other body fluids or regions are also preferred.²³⁻²⁵

In our study, we found that the use of local anesthetic will facilitate nasopharyngeal sampling, both for the patient and for the healthcare personnel. For patients, less pain and more comfort during sampling may be a cause to overcome the prejudgments and barriers to testing.¹¹ For healthcare workers, sampling performed in a shorter time and without more repetition, patients' resistance and/or undesirable reactions, may reduce the workload and transmission caused by sampling.^{7,13}

It may be thought that the application of local anesthetic before sampling may increase the waiting time of the patients for the test. This is important because suspected cases staying together for too long will increase the risk of COVID-19 transmission to potential negatives during testing.²⁶ However, our findings showed that only a 5-minute wait may provide adequate anesthesia. Also, lidocaine, which we used as the local anesthetic in our study, is easily available, and its intranasal application is a safe option.^{15,27} The most important reason for choosing lidocaine in our study is its short-acting effect as well as its sufficient effect during the procedure.²⁸ Local anesthetics reduce pain by binding voltage-gated sodium channels and blocking the excitation threshold of nociceptive afferent neurons, and inhibit the inflammatory cascade in the dorsal horn of the spinal cord, which sensitizes the free-end nociceptor, thereby reducing excessive excitability.²⁹ A long-acting nasopharyngeal local anesthetic may increase the risk of adverse effects such as aspiration pneumonia due to ingestion of drug downward from the nasopharynx, and the risk of other systemic side effects.^{29,30} This may create significant controversy in particular for COVID-19, the most important clinical presentation of which is pneumonia.

Limitations

This study has several limitations. The first is that the study is a single-center study with relatively small sample size. This negatively affects the external validity of the study. On the other hand, because the study was conducted with healthy volunteers, we cannot say exactly that lidocaine will provide similar effects in the “real” patients. In placebo-controlled studies, “the placebo effect” may be an essential confounder. In our study, we repeated the nasopharyngeal sampling twice, before and after the intervention, to get ahead of this potential bias. The results show us that there is no significant placebo effect in our study design. On the other hand, we did not evaluate the effect of lidocaine or isotonic saline application on the result of the test, such as PCR. However, the aim of our study is only to examine the convenience of lidocaine in the application of nasopharyngeal swab, Kanodia et al.¹⁶ reported that oropharyngeal lignocaine application for oropharyngeal swab sampling did not change the SARS-CoV-2 viral load in RT-PCR test of the COVID-19 patients.

Conclusion

Considering that its effect on diagnostic test such as PCR has not been evaluated, intranasal lidocaine application reduces the pain that occurs during nasopharyngeal sampling and makes the procedure easier for the patient and the healthcare worker. Studies with broad participation in which the effects of the use of local anesthetics before sampling on diagnostic tests such as PCR are also investigated, may pave the way for developments in this area.

Declarations

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Author contributions

Conceptualization, K.A.O. and C.Z.; Methodology, D.S. and T.D.; Software, D.S.; Validation, T.D., C.Z.; Formal Analysis, D.S.; Investigation, K.A.O.; Resources, I.A.; Data Curation, D.S.; Writing – Original Draft Preparation, T.D.; Writing – Review & Editing, I.A. and T.D.; Visualization, C.Z.; Supervision, C.Z.; Project Administration, K.A.O.

Conflicts of interest

The author(s) declare no competing interests.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

The study was conducted following the CONSORT guideline and the tenets of the Declaration of Helsinki at our Emergency Department between 01.09.2020 and 30.09.2020 after obtaining the approval of the Atatürk University Clinical Research Ethics Committee. We have been registered in a clinical trial database (ClinicalTrials.gov Identifier: NCT04885777). Also, the written informed consent of all participants was obtained.

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