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ORIGINAL RESEARCH

Effect of 2% Topical Lidocaine Gel on Discomfort from Electrical Stimulation During Nerve Conduction Studies- A Prospective Double-Blind Placebo-Controlled Study

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Purpose: Procedure discomfort can limit electrodiagnostic studies. Reducing discomfort can maximize the benefits of these diagnostic tools. This study targeted the discomfort associated with nerve conduction studies (NCS).

Patients and Methods: This was a prospective randomized double-blind placebo-controlled study comparing the effect of topical lidocaine gel (2%) versus analgesic-free lubricant gel (K-Y gel) on pain perception during NCS. Sequential patients (n=130) referred for routine NCS participated in the study. We applied 1 mL of lidocaine gel to one palm, and 1 mL of K-Y gel to the other as a control. After 20–45 min of application, graded increments of electrical stimulation intensity were delivered to record the median and ulnar mixed palmar nerve responses. Patients were then asked to score the degree of pain felt from electrical stimulation over each palm using the Wong-Baker Faces Pain Scale (WBFPS) and the Numeric Rating Scale (NRS), independent of baseline pain.

Results: Mean WBFPS and NRS scores for lidocaine-treated palms were significantly lower than those for controls using parametric paired *t*-test (3.79 vs 4.37 and 3.35 vs 3.78 respectively, all p-values<0.05). Subgroup analysis showed a significant decrease in mean scores in females, patients aged ≤50 years, patients without a history of previous NCS, and patients without comorbidities (all p-values<0.05). Median scores using nonparametric Wilcoxon ranked test also showed statistically significant differences (all p-values<0.05).

Conclusion: The results indicate that topical lidocaine 2% gel reduces discomfort associated with NCS. However, despite the statistical significance, clear clinical significance may be lacking. Clinical implementation may be considered for the subgroups that showed the greatest benefit. Further studies that incorporate more efficient drug delivery methods may yield better results.

Keywords: topical lidocaine, nerve conduction study, discomfort, electrodiagnostic

Introduction

Nerve conduction studies (NCS) and electromyography (EMG) are essential components of the electrodiagnostic examination for assessing many neuromuscular disorders.[1] Pain has frequently been considered a major pitfall in EMG.[2,3] NCS, on the other hand, are considered safe and well tolerated with no long-term adverse effects; however, they are frequently associated with discomfort (from electrical stimulation)[4] that, from our experience, may occasionally lead to the premature termination of the procedure. Discomfort and pain can be significant contributors to suboptimal patient cooperation.[2,5] This may also ultimately affect patients' willingness to undergo the procedure a second time in the future and the likelihood that they will recommend the procedure to others. Many factors may contribute to the discomfort encountered during a procedure, including

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procedural anxiety level,[2,6] sex,[6] and the interaction between patients and the person performing the study.[7] In general, pain expectation during electrodiagnostic testing is thought to be more exaggerated for EMG than for NCS procedures.[8]

Reviewing the literature revealed many studies investigating the reduction of pain and discomfort during EMG using different techniques and agents, such as oral and topical formulations.[9–11] However, studies aiming at reducing the discomfort associated with NCS are limited. Topical lidocaine has been helpful in the management of neuropathic pain.[12–14] Its limited systemic absorption is a particularly attractive option in elderly patients and in those taking multiple medications, as the risk/benefit ratio becomes more favorable in such patients. In this study, we aimed to evaluate whether topical lidocaine 2% gel can reduce the discomfort associated with NCS.

Methods

This was a prospective randomized double-blind placebo-controlled study. It was approved by the Institutional Review Board (IRB number 2/128/2019) and by the Human Research Ethics Committee and conformed to the Declaration of Helsinki. The study subjects were sequential patients aged ≥ 16 years who were referred to the clinical neurophysiology lab at our hospital for NCS. Excluded patients were those with significant comorbidities such as severe cardiac or pulmonary diseases; patients who were acutely ill; patients with a previous history of drug allergies; patients taking medications that affect pain perception; patients referred for a condition that does not require NCS of the hands; and patients with significant liver or renal diseases, as these may affect the metabolism of the study drug and potentially increase systemic adverse effects. The study aims and steps were explained to all patients, and those who agreed to participate were asked to sign an informed consent form. The main comorbidities that were present in the included patients were systemic arterial hypertension, diabetes mellitus (DM), mild ischemic heart disease, hypothyroidism, and degenerative disc disease. Most of the included patients were referred to rule out carpal tunnel syndrome (CTS). Other referral diagnoses were peripheral neuropathy, cervical radiculopathy, and brachial plexopathy. For all participants, we applied 1 mL of lidocaine 2% gel to one palm using a syringe and applied 1 mL of K-Y gel to the other palm as a control agent. The gel was applied to either the right or the left palms in a random fashion and was rubbed lightly to cover the entire palm. To help minimize early drying, plastic gloves were worn by the study subjects during the application period which ranged from 20–45 min, after which the gloves were removed, and the gel was wiped off with a dry gauze. Immediately after that, a second investigator performed the NCS and delivered electrical stimulation orthodromically to one palm with graded intensity increments of 3–5 mA at a constant pulse width of 0.1 msec until supramaximal stimulations of the median and ulnar mixed palmar nerves were reached. Recording electrodes were placed at the wrist 8 cm proximal to stimulation points. The same stimulation protocol was replicated on the contralateral palm until the same maximum stimulation intensity that was delivered to the first palm was reached. Both the patient and the second investigator performing the electrical stimulation were blinded to the type of gel that was applied to each palm. The patients were asked to score the discomfort/pain they felt from stimulating each palm using the Wong-Baker Faces Pain scale (WBFPS) and the Numeric Rating Scale (NRS) immediately after stimulating both sides and before completing the NCS for which they were referred. Standard safety measures were followed, according to our hospital and neurophysiology laboratory policies.

The sample size of the participants in the study was selected based on conducting a power analysis. First, a pilot study on 70 participants was conducted, and the difference in pain was computed for each patient. The results revealed a standard deviation in the differences scores of approximately 1.648 units. A detectable difference of 0.5 units with a 95% target test power of one-sided test of hypothesis at $\alpha = 0.05$ was selected. Power analysis provided a required sample size of 119 participants with an actual test power of 0.950094. Because of the factors affecting the errors in sample size determination such as sampling error in estimation, we have slightly increased the sample size of n=119 to n=130. Power curve is shown in Figure 1. The flow diagram of the statistical plan and design is shown in Figure 2.

Statistical Methodology

We used the parametric paired *t*-test and the nonparametric Wilcoxon ranked test for the comparison of the mean and median scores of WBFPS and NRS between palms treated with lidocaine gel (treatment) and palms treated with K-Y gel (control). All P-values presented were one-sided hypothesis to test if there was a significant decrease in the mean and median pain scores in the treatment group compared to the control group. Statistical significance was set at $p < 0.05$.

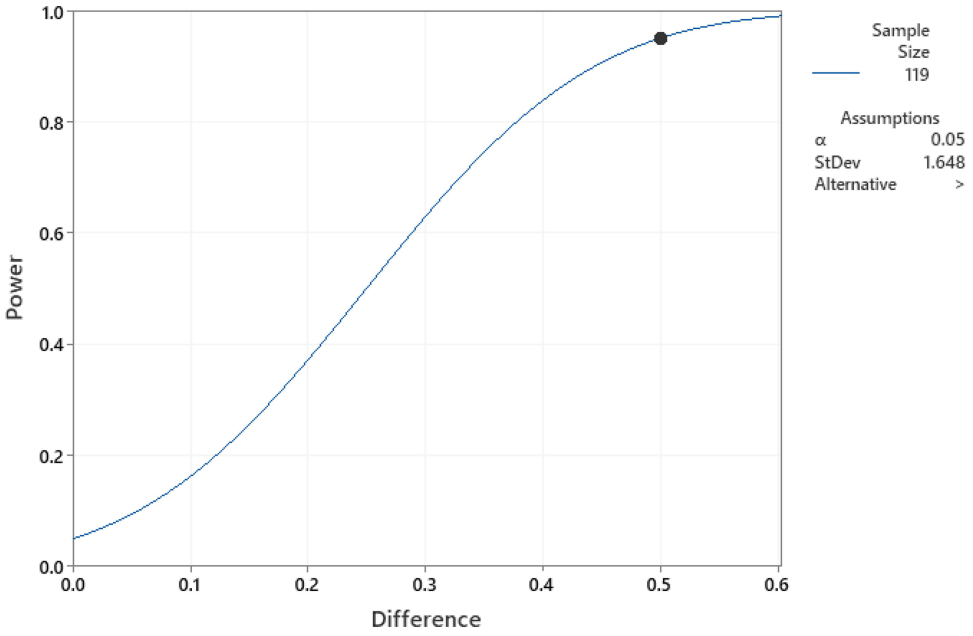

Figure 1 Sample size calculation and power curve.

Statistical Package for Social Sciences version 21 software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. Jupyter Notebook version 6.0.3 was used to produce the bar chart plots.

Results

Study Subjects and Pain Scores

A total of 130 patients were enrolled in this study. Of those, 91 were females (70%) and 39 were males (30%). The patients' age range was 19–72 years, with a mean ± SD of 44.65 ± 12.07 years. Summary of the demographic information of the subjects in the study is shown in Table 1. In the statistical analysis, both the parametric paired *t*-test and nonparametric Wilcoxon ranked test were used (Tables 2–4). The means and medians of the WBFPS and the NRS scores for lidocaine-treated palms were significantly lower than those for controls at different characteristics considered in this study (all p-values < 0.05).

Pain Scores and Other Variables

The paired *t*-test and the Wilcoxon ranked test were also used to calculate the differences in WBFPS and NRS scores between lidocaine and K-Y in relation to other variables such as sex, age, history of previous NCS, and presence of comorbidities to identify subgroups with the highest benefit/response to lidocaine gel. For both WBFPS (Table 3) and NRS (Table 4), the results showed a significant decrease in the mean and median scores for lidocaine compared to K-Y for the categories of females, patient age ≤ 50 years, negative history of previous NCS, and lack of comorbidities. A visual examination of the data using error bar plot using numeric rating scale of control and treatment is shown in Figure 3 and error bar plot using Wong-Baker faces pain scale of control and treatment is shown in Figure 4.

Neurophysiological Outcomes

The majority of participants had either unremarkable or non-lateralizing findings after completing their neurophysiological studies (Table 5). A total of 43 participants had neuropathic findings that were either unilateral or worse in one limb compared to the other. The more neuropathic side received lidocaine in 20 participants and K-Y in 23 participants. The electrical stimulation intensity applied to both sides was equal as per study design with a mean ± SD of 38.3 mA ± 16.05.

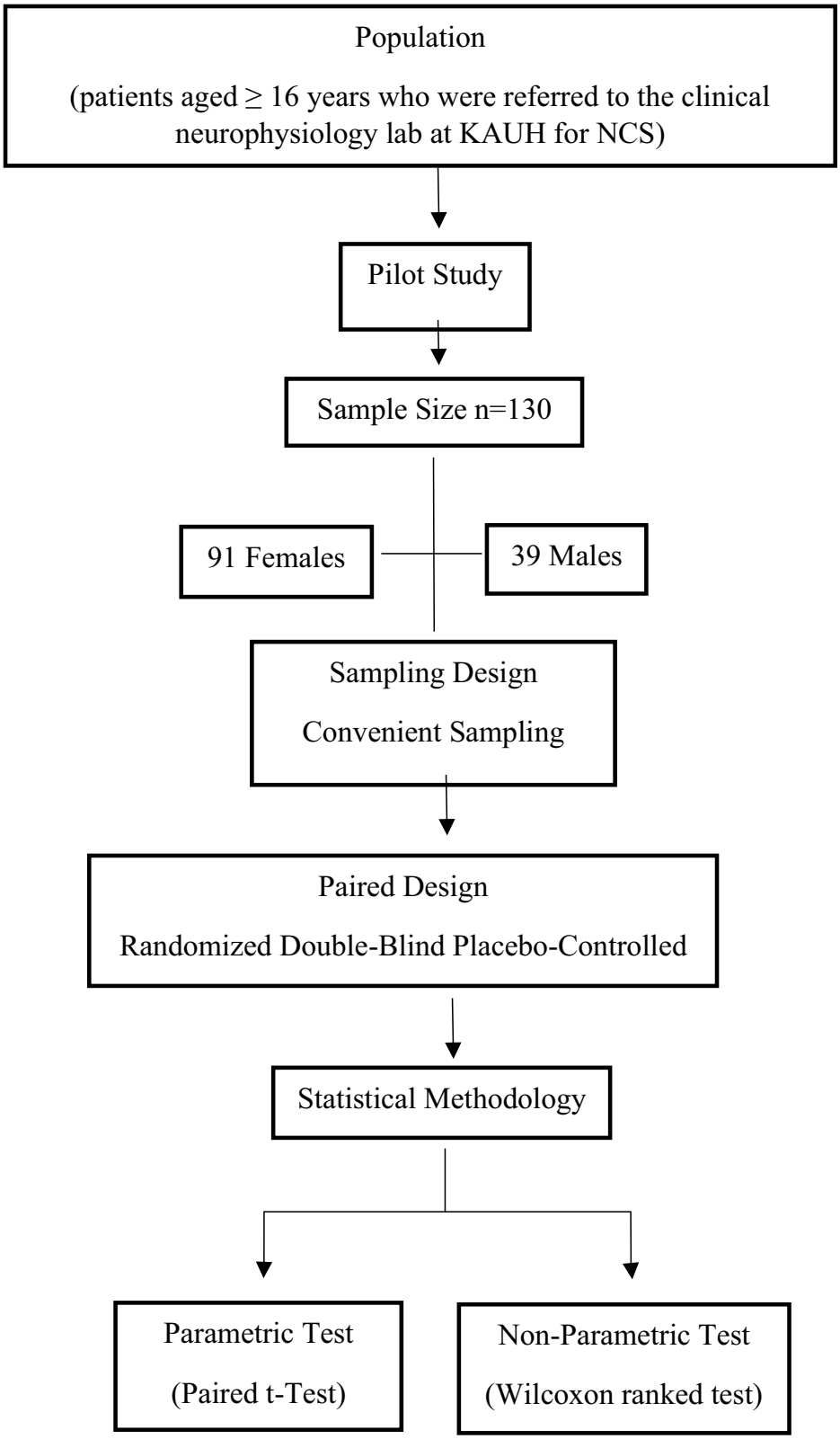

Figure 2 Flow diagram of design and statistical plan.

Table 1 Summary of the Demographic Information of the Subjects in the Study

Variable	Absolute	%
Age: Mean± SD	44.65±12.07	–
Gender		
Male	39	30
Female	91	70
Marital Status		
Single	19	14.62%
Married	109	83.84%
Divorced	1	0.77%
Widow	1	0.77%
Education Level		
Illiterate	5	3.84%
High school or less	42	32.31%
More than High school	83	63.85%

Table 2 Summary Statistics and Results of Paired *t*-test and Wilcoxon Ranked Test of Treatment and Control Groups for the Study Subjects Using Wong-Baker Faces Pain Scale and Numeric Rating Scale

Scale	n	Lidocaine		K-Y		Paired t-test	Wilcoxon Ranked Test
		Mean	S.D	Mean	S.D	P-value	P-value
Wong-Baker Faces Pain Scale	124	3.79	2.35	4.37	2.57	0.008**	0.013*
Numeric Rating Scale	130	3.35	1.82	3.78	1.99	0.004**	<0.001**

Notes: *Indicates statistical significance at $\alpha = 0.05$, **Indicates statistical significance at $\alpha = 0.01$.

Table 3 Summary Statistics and Results of Paired *t*-test and Wilcoxon Ranked Test of Treatment and Control Groups in Relation to Sex, Age, History of NCS, and Comorbidities Using the Wong-Baker Faces Pain Scale

Variable	n	Lidocaine		K-Y		Paired t-test	Wilcoxon ranked test
		Mean	S.D	Mean	S.D	P-value	P-value
Sex							
Female	87	3.79	2.38	4.39	2.49	0.014*	0.022*
Male	37	3.78	2.30	4.32	2.77	0.141	0.135
Age							
≤ 50	85	3.84	2.43	4.61	2.64	0.008**	0.011*
> 50	39	3.69	2.18	3.85	2.35	0.301	0.341
History of NCS							
YES	39	3.95	2.61	4.00	2.64	0.452	0.420
NO	77	3.66	2.28	4.49	2.58	0.004**	0.005**
Comorbidities							
YES	44	3.86	2.26	4.32	2.89	0.122	0.178
NO	60	3.70	2.41	4.43	2.50	0.017*	0.020*

Notes: *Indicates statistical significance at $\alpha = 0.05$, **Indicates statistical significance at $\alpha = 0.01$.

Table 4 Summary Statistics and Results of Paired *t*-test and Wilcoxon Ranked Test of Treatment and Control Groups in Relation to Sex, Age, History of NCS, and Comorbidities Using the Numeric Rating Scale

Variable	n	Lidocaine		K-Y		Paired *t*-test	Wilcoxon Ranked Test
		Mean	S.D	Mean	S.D	P-value	P-value
Sex							
Female	91	3.27	1.87	3.66	1.97	0.015*	0.014*
Male	39	3.51	1.70	4.05	2.03	0.063	0.079
Age							
≤ 50	90	3.36	1.86	3.88	2.09	0.005**	0.007**
> 50	40	3.33	1.73	3.55	1.74	0.210	0.207
History of NCS							
YES	39	3.18	2.01	3.51	1.99	0.133	0.179
NO	83	3.34	1.73	3.83	2.04	0.010**	0.011*
Comorbidities							
YES	45	3.16	1.64	3.60	1.96	0.063	0.069
NO	64	3.41	1.96	3.86	2.02	0.022*	0.017*

Notes: *Indicates statistical significance at $\alpha = 0.05$, **Indicates statistical significance at $\alpha = 0.01$.

Discussion

In this study, we used lidocaine 2% gel to assess whether it has beneficial effects on reducing discomfort encountered from electrical stimulation in NCS. To the best of our knowledge, this is the first study to evaluate the effects of topical lidocaine on NCS discomfort. Topical lidocaine is a local anesthetic agent that is widely used in multiple medical procedures and in pain management for a variety of conditions.[15,16] It acts by binding to voltage-gated sodium channels on the inner surface of the neuronal cell membrane, leading to a decrease in the influx of sodium ions, which inhibits depolarization and ultimately leads to the blockage of conduction.[15] Lidocaine gel has a rapid onset of action that is within 3–5 min when applied to mucus membranes, but has poor absorption through intact skin.[15,16] Different topical formulations have variable skin absorption rates, and therefore, variable onsets of action ranging from about 25 min to more than 90 min. Additionally, the effect may vary with the site of application and the level of analgesia that is pursued.[17] The adverse effects of lidocaine gel are essentially limited to mild local skin reactions if applied to intact skin, which seems to be related to the duration of the application and the concentration being used.[16,18,19] In this study, we applied lidocaine gel as a treatment agent and K-Y gel as a control agent to the same study subject but on opposing palms and used the WBFPS and NRS to compare differences in perceived pain/discomfort between both sides. This approach helped eliminate most of the confounding factors that could have affected and limited the interpretation of the results, thereby increasing the power of the study.

The WBFPS and NRS are frequently used to evaluate the degree of pain. Usually, both scales are treated as ordinal scales in which nonparametric statistical methods are used in the statistical analysis. However, in pain research, there has been debate regarding whether the WBFPS should be treated as an ordinal scale or as an interval scale. In certain occupations, the WBFPS was assumed to be an interval scale, and the NRS was considered a ratio scale; thus, parametric statistics can be used in the statistical analysis.[20–22] Some investigators argued that parametric statistics can be applied even if the data are composed of ordinal scales under the assumption that the data are normally distributed or when the sample size is large as per the central limit theorem.[23,24] Others reported that the parametric *t*-test or the ANOVA test can be applied to the WBFPS without inflation of the type-1 error.[25] In statistical analysis, statisticians and researchers prefer using parametric tests because, in general, they are more powerful than nonparametric tests. The statistical analysis in this study involved the use of both parametric and nonparametric tests. The results showed that both parametric and nonparametric tests revealed similar results in terms of statistical significance.

Both the WBFPS and NRS scores were lower in lidocaine-treated palms than in K-Y–treated palms ($p < 0.05$). This indicates that lidocaine has beneficial effects on reducing discomfort during NCS. Upon subgroup comparisons, we found

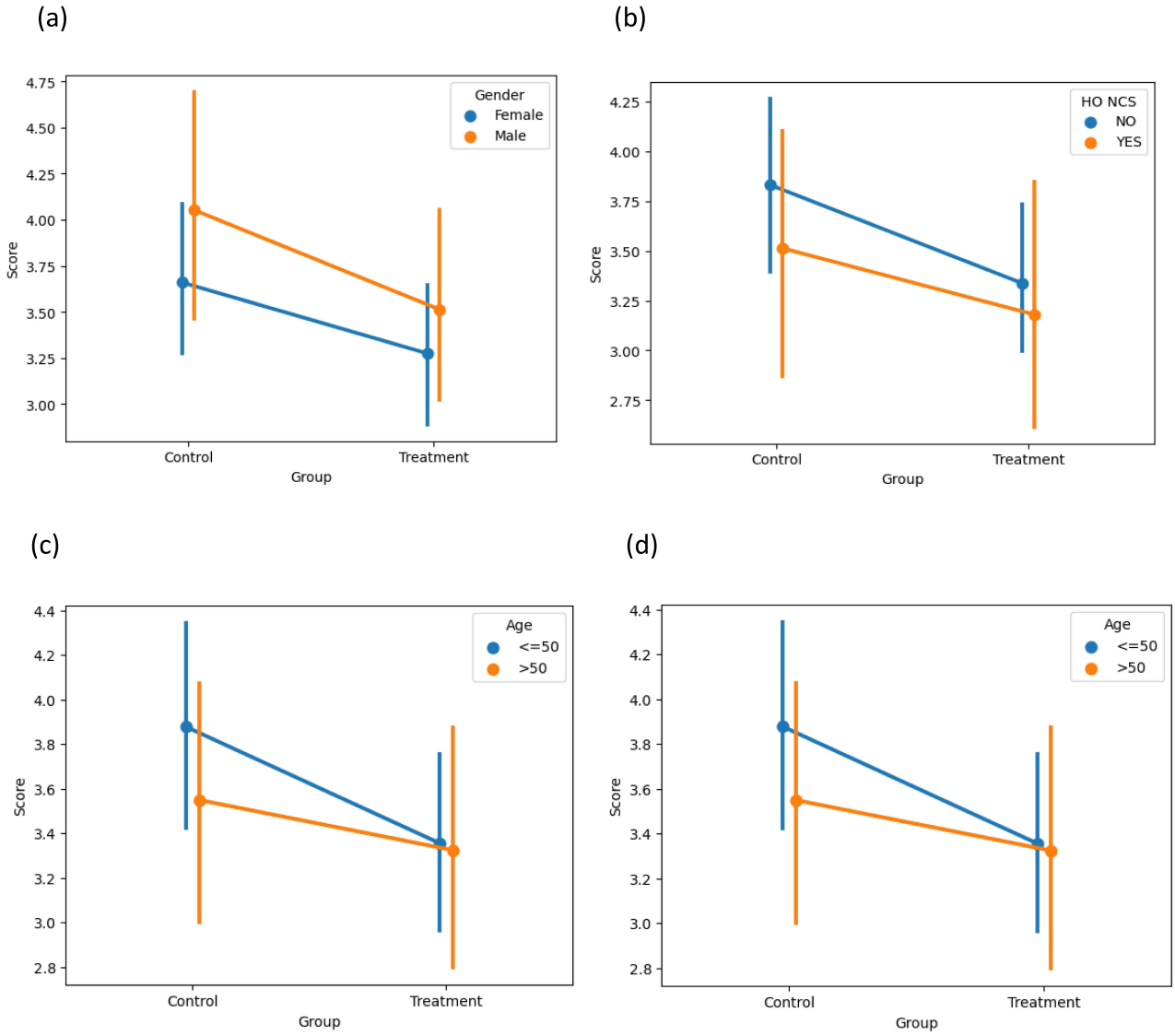

Figure 3 Error bar plot using numeric rating scale of control and treatment in relation to (**a**) gender (**b**) history of NCS (**c**) age group (**d**) health status.

that both scores were significantly lower for lidocaine-treated palms than for control palms in females, patients ≤ 50 years of age, patients without comorbidities, and patients undergoing NCS for the first time.

It has been reported that female skin is thinner than male skin and androgens account for why a man's skin is about 20% thicker than that of a woman.[26] Additionally, the dermis layer, which contains the free nerve endings responsible for pain sensation, is thinner in the palms of females compared to that in males.[27] Therefore, these variations may have contributed to the clearer effect in females.

In this study, we relied on the patient's ability to try to differentiate between the pain/discomfort felt over one palm from that over the other and from disease-related pre-procedure pain. This was particularly more difficult to clarify to elderly patients despite great attempts to explain the procedure in detail. Older age groups have a wide range of life experiences and cultural backgrounds that might affect their perception of diseases, willingness to follow medical protocols, and ability to communicate effectively.[28,29] Additionally, the normal aging process may involve sensory loss, reduced memory, and slower processing of information.[30] These factors may explain why the response was clearer in patients aged ≤ 50 years.

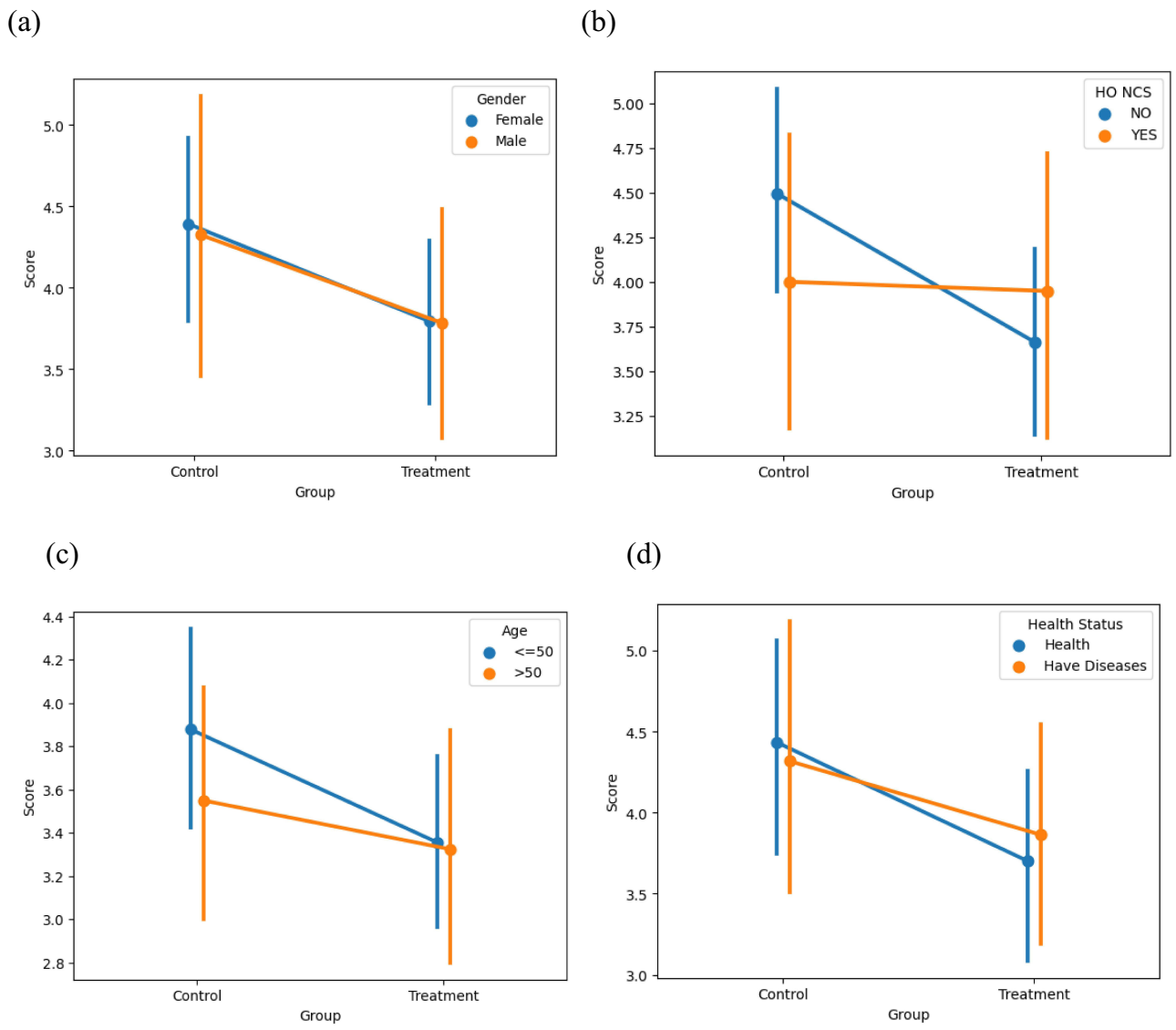

Figure 4 Error bar plot using Wong-Baker faces pain scale of control and treatment in relation to (**a**) gender (**b**) history of NCS (**c**) age group (**d**) health status.

The scores were also lower in lidocaine-treated palms than in control palms in patients without comorbidities. Previous studies have shown that certain chronic diseases might affect pain perception and influence a patient's response.[31–33] It has also been reported that lidocaine efficacy decreases in the presence of inflammation or in conditions

Table 5 Final Neurophysiological Diagnosis of Participants at Study Completion

Neurophysiological Diagnosis	Patients (n)	Lidocaine Applied to the More Affected Side (n)	K-Y Applied to the More Affected Side (n)
Normal study	56	–	–
Bilateral CTS	28	–	–
PNP	3	–	–
Unilateral CTS/worse CTS on one side	34	15	19
Unilateral other (radiculopathy, plexopathy, mononeuropathy)	9	5	4

with increased production of inflammatory mediators.[34] These findings may explain why the benefit was more evident among patients without comorbidities.

In patients undergoing NCS for the first time, it is difficult to ascertain the cause of the beneficial effect of lidocaine. A lower percentage of this group had a premorbid condition than those who had a previous NCS (31% vs 38%). Additionally, it is reasonable to assume that patients who had a previous NCS suffered from a more chronic disease course or had other comorbidities, as evidenced by the need to repeat their NCS. These factors would favor a beneficial response to lidocaine, as explained above. However, more data pertaining to pre-procedure pain, anxiety level, and patients' experiences during previous NCS should be looked into for a better assessment.

While EMG studies are generally considered uncomfortable/painful,[2,3] it was found that patients had a wide range of tolerance for the needle exam during EMG studies as the reported pain ranged from 0 (none) to 9 (10 being most severe) in one study.[7] Similarly, the reported pain in our study using the NRS ranged from 0–10 for the control side and 0–9 for the treatment side; the range was 0–10 for both sides using the WBFPS. This indicates that for some patients, NCS can be as uncomfortable as EMG studies, which may be related to patients' expectations of pain prior to the procedure,[8] the intensity of maximal stimulation reached, and the total examination time.[4] Interestingly, the mean NRS scores were slightly lower in females than in males (3.27 vs 3.51) (Table 4). This is different from what has been reported in previous EMG-related studies, where the female sex was associated with higher reported pain scores.[6,35]

Other factors that impact pain/discomfort perception are the number and intensities of electrical stimuli delivered to each palm. By applying the same incremental stimulation protocol to both palms, we ensured that each side received a fairly comparable number of stimulations. Moreover, the maximum stimulation intensity delivered was identical for both sides for the purpose of pain scoring. We reached supramaximal stimulation on the first tested palm and reached the same maximum intensity value on the contralateral side, regardless of being supra- or submaximal. This ensured that the scoring of pain was based on a comparable stimulation intensity experience irrespective of that from the post-scoring completion of the NCS procedure for which the patients were referred.

Limitations

Although our findings regarding the effect of topical lidocaine in reducing discomfort during NCS were statistically significant, clear clinical significance may be lacking. The minimum clinically significant difference in NRS scores was previously estimated to be in the range of 1.39–1.5.[36–38] This lack of clinical significance may be attributed to numerous factors. The application of lidocaine to the palm, which has thick skin, is more likely to make absorption less efficient than if lidocaine is applied to thinner skin such as the forearm or leg skin. In addition, the thenar skin has a higher perception sensitivity to pain than the forearm skin.[10] This higher sensitivity may have affected the patients' ability to discriminate minor differences in pain levels between both palms. Additionally, the study subjects' baseline pain and anxiety levels were not recorded prior to the procedure, which may have influenced the subjects' responses and potentially contributed to a reduction in the expected analgesic effect of lidocaine. Other investigators showed that 8% lidocaine yielded a more robust effect on pain threshold over face and hand skin than the yield of 2% lidocaine.[39] Therefore, the use of higher concentrations of topical lidocaine may result in greater pain relief. We could have attempted to increase the waiting time after the application of lidocaine beyond 45 min, but this would make it less applicable in everyday practice. Another concern is that topical lidocaine gel, with its conduction-blocking ability, may interfere with the nerve conduction parameters that we measure. However, the limited skin absorption coupled with the relatively deep location of the nerves undergoing stimulation and the ultimately diluted lidocaine concentrations reaching these nerves make this interference a remote possibility. It is reasonable to expect that the skin treated with topical lidocaine gel would become significantly anesthetized before a relevant impact on the deeper nerve trunks is detected. Significant skin anesthesia was not reported in our cohort of patients and is not typically observed in clinical practice.

Conclusion

The findings of this study demonstrated a significant decrease in pain scale scores for topical lidocaine-treated palms versus control palms, indicating that lidocaine 2% gel reduces discomfort associated with NCS. This reduction was most evident in the female sex, in the age group of 50 years or younger, in patients without comorbidities, and in patients undergoing the NCS

for the first time. However, despite the statistical significance, the results may not be sufficient to be translated into clinical significance. Consideration of clinical implementation may be warranted for apprehensive patients from any of the above-mentioned subgroups that showed the greatest benefit. Further studies using higher concentrations of lidocaine, different formulations with higher absorbability, different durations of analgesic application, and the application of lidocaine to non-palmar skin sites may yield better results.

Ethic Statement

The study was approved by the Institutional Review Board (IRB) of Jordan University of Science and Technology (IRB number 2/128/2019) and by the Human Research Ethics Committee of King Abdullah University Hospital and conformed to the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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