Original Article

Efficiency of 90-Min Extended EMLA-Induced Stimulated Skin-Wrinkling Test in the Diagnosis of Carpal Tunnel Syndrome

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Abstract

Background: Previous researchers have used a 30-min eutectic mixture of local anesthetic (EMLA) test, which assesses the sympathetically mediated vasomotor function, in diagnosing carpal tunnel syndrome (CTS). However, its specificity was low, limiting its clinical diagnostic utility. In this study, we assessed the efficiency of 90-min extended EMLA-induced stimulated skin-wrinkling (SSW) test in CTS diagnosis. **Methods:** A cross-sectional study was designed among patients clinically diagnosed with CTS. Hands of healthy volunteers and the asymptomatic hands of selected patients served as control. The Boston symptom severity scale (SSS) and the neuropathic pain severity inventory (NPSI) were used to assess symptom severity, and nerve conduction study (NCS) was used to assess electrophysiological severity. EMLA-induced SSW was visually graded after 90 min of application and correlated with symptom and NCS severities. **Results:** Forty-two symptomatic hands and 30 asymptomatic hands were enrolled as cases and controls, respectively. The diagnostic efficiency of the extended EMLA test was found to be 83.4% for digit 2 and 87.3% for the lateral 4 digits (mean), whereas the diagnostic efficiency of standard NCS was 88.1%. Boston SSS and NPSI were better correlated with EMLA positivity than NCS positivity. A linear regression analysis showed negative correlation of wrinkling grade with NCS grade. **Conclusion:** With its improved diagnostic efficiency, the 90-min extended EMLA test can feasibly be used as an alternative to NCS, especially in general practice settings. Its potential clinical utility should be explored in a large population of CTS patients showing varying clinical and electrophysiological severities.

Keywords: Carpal tunnel syndrome, EMLA, nerve conduction study, small-fiber neuropathy, stimulated skin wrinkling

Introduction

Nerve conduction study (NCS) is considered to be the single most useful investigation for the diagnosis of carpal tunnel syndrome (CTS).[1] However, it is widely observed that in many patients with CTS, there is no correlation between clinical and electrophysiological severity.[2,3] This apparent clinical and electrophysiological dissociation is attributed to the fact that conventional NCS only assesses large-fiber (A-beta) demyelination or axonal loss and fails to assess small-fiber dysfunction.[4] In addition to the large A-beta fibers that carry non-nociceptive sensations, the median nerve trunk across the carpal tunnel also carries small myelinated (A-delta) fibers which carry most of the nociceptive and thermal sensations and unmyelinated C-fibers, which serve as the postganglionic sympathetic fibers mediating sudomotor and vasomotor functions.[4] Many previous researchers report that small fibers, including sympathetic fibers (unmyelinated C fibers), are not only affected in most patients with CTS but also affected much earlier.[5] Thus, in many patients with early CTS with predominant small-fiber involvement, in spite of severe symptoms, conventional NCS will be normal or show only minimal changes.

Many investigations have been used for evaluation of small-fiber dysfunction, of which sympathetic skin response which assesses the sudomotor function has been used in the diagnosis of CTS, but their sensitivity was found to be low.[6,7] Intra-epidermal nerve fiber density (IENFD) evaluation by skin biopsy is considered the gold standard.[8] However, this method is invasive and requires access to a specialized histology facility that is often not readily available in clinical practice.

It is widely known for several years that immersing the hand in water for some time will result in wrinkling of the permeable palm skin.[9] The underlying mechanism was found to be vasoconstriction of the digital vasculature mediated via sympathetic nerve fibers and has been used as an indicator of limb sympathetic nerve function.[10] Recently, a few researchers substituted water with a eutectic mixture of local anesthetic (EMLA), which also, by the same mechanism, induces skin wrinkling after 5–30 min of topical application, and suggested this as a simple and practical bedside test to assess sympathetic function.[11] This stimulated skin

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Submitted: 09-Apr-2021 **Revised:** 07-Aug-2021 **Accepted:** 25-Aug-2021
Published: 07-Dec-2021

DOI: 10.4103/aian.aian_305_21

wrinkling (SSW) was also found to correlate well with abnormal IENFD indicating small-fiber damage.[12]

Recently, a few researchers assessed EMLA-induced vasomotor dysfunction in CTS by measuring blood flow velocity changes[13] and by visual inspection and grading of the EMLA SSW[14] after 30 min of topical EMLA application. Fairly high sensitivity was reported for this test; however, the specificity was found to be much lower, thus limiting its clinical diagnostic utility.[14] Bjerring *et al*.[15] observed that in healthy subjects, the EMLA cream produces maximum vasoconstriction after 90 min of application. However, after prolonged application (≥ 3 h), its smooth muscle relaxant effect causes vasodilatation.

In this paper, we assessed whether sensitivity and specificity of this test for CTS can be improved by extending the application time to 90 min. We also analyzed the correlation of SSW grade with CTS symptoms and electrophysiological severity. Further, we examined whether, in hands affected with CTS, vasomotor disturbance and the resultant skin wrinkling exactly follow the conventional median nerve innervation pattern (lateral three and a half digits).

Methods

A cross-sectional study was designed among consecutive patients aged between 25 and 55 years who attended the outpatient clinics with symptoms suggestive of CTS from October 1, 2020, to January 31, 2021. The asymptomatic hands of patients and hands of age and gender-matched healthy persons who volunteered to be included in the study formed the control group.

The diagnosis of CTS was based on the Clinical Diagnostic Criteria for CTS Research proposed by the American Association of Electro Diagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation.[16] Personal data of each participant including age, gender, handedness, occupation, and educational status were documented. Further, history of systemic illnesses, if any, and medication history were recorded.

Only idiopathic CTSs (with absent etiologic clues[17] except age, high BMI, and jobs involving high intensity of wrist and hand activity) were included. No participant in both case and control groups had any systemic illnesses including diabetes, thyroid disorders, hepatic and renal disease, cardiovascular disorders, and cardiac failure. Patients with symptoms suggestive of generalized peripheral neuropathy, including tingling and numbness in the lower limbs, and those with autonomic symptoms were also excluded. No patients with neck pain, shoulder pain, history of sympathectomy, and those with history of significant trauma to upper limbs were included. No participant had HIV and Hansen's disease. All patients with severe anemia, alcoholism, concomitant therapy with anticholinergic, α- and β-adrenergic antagonist, or other medication that could interfere with testing of autonomic function were excluded. No pregnant or lactating women were included in this study. Patients with rough palmar skin and callosities were also excluded.

The whole process was explained to the patients and those who expressed difficulty to come and stay for 2 h in the outpatient department on another day for the EMLA test were excluded from the study. The study was approved by the Institutional Research and Ethics Committee (Ref. no. 11/IEC/21/AIMS–58) and all participants gave informed written consent before participating.

Symptom assessment

The symptom distribution of the symptomatic hands was recorded with the Katz Hand Diagram.[18] For assessing symptom severity, we used the validated regional language version of the instruments – symptom severity subscale of the Boston Carpal Tunnel Questionnaire (BCTQ SSS)[19] and the neuropathic pain symptom inventory (NPSI).[20] With NPSI, we assessed and quantified different dimensions of neuropathic pain which included burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. Each of these items was quantified on a (0–10) numerical scale.

Further, additional symptoms like swelling, itching, trophic skin changes, etc., and any sensory impairment of the hand in the median distribution, and any weakness and wasting of the thenar muscles were recorded.

Electrophysiological evaluation

Electro-diagnostic studies were performed as per the AANEM practice recommendations for CTS.[21] Standard studies were done in all participants. This included median and ulnar sensory and motor conduction studies on both sides. Median and ulnar antidromic sensory studies were done with stimulation at the wrist 14 cm proximal to the recording electrode (G1) placed on digits 2 and 5. Patients with electrophysiological evidence of ulnar neuropathy were excluded. Peroneal and tibial motor and superficial peroneal and sural sensory studies were performed if there were any symptoms suggestive of a generalized neuropathy, and if abnormal, such patients were also excluded.

If standard NCS was normal, two comparison studies (median – ulnar/radial) were done as per the guidelines,[16,21] and if these two comparison studies did not clearly agree, combined sensory index (CSI)[22] was calculated (CSI ≥1 was taken as abnormal). Motor and sensory nerve conduction studies were performed with Viking IV (Nicolet, Madison, Wisconsin, USA) using standard techniques.[23]

During the electrophysiological examination, skin temperature (mid-palm) was measured using attached temperature probes to ensure temperature above 32°C, and if found to be low, an IR warmer was used to bring the temperature above 32°C.

Patients were classified into six severity grades (Grade 1: very mild CTS, Grade 2: mild CTS, Grade 3: moderately severe CTS, Grade 4: severe CTS, Grade 5: very severe CTS, and Grade 6: extremely severe CTS) based on the neurophysiological grading proposed by Bland.[24]

EMLA testing

EMLA, a local anesthetic cream, is a eutectic emulsion of lidocaine and prilocaine in the ratio of 1:1 (lidocaine 2.5%, prilocaine 2.5%). It is observed that EMLA causes vasoconstriction of the digital pulp vasculature resulting in loss of pulp volume, which results in the skin overlying the digital pulp being pulled down by negative pressure created inside the digit pulp. As a result, reversible undulations (wrinkling) develop in the skin of the palms and soles after 5–30 min of exposure. Individuals with small-fiber neuropathy will have sympathetic vasomotor dysfunction and will not display this SSW.[25]

After the electrophysiological evaluation, patient was requested to come for the EMLA test on the next working day. Two hours prior to the test and throughout the testing period, the participants were instructed not to use any other skin creams and to abstain from smoking and consuming caffeinated beverages. After cleaning the hands with soap and water, a pre-EMLA photograph of the hand and digits was taken. Then, EMLA cream was applied thickly and uniformly on the pulp of all fingers of the selected hands. After that, a thin layer of cotton was applied over the cream and covered with a micropore adhesive tape. Mid-palm temperature was taken with a digital infrared thermometer to ensure temperature above 32°C. At the end of 90 min, the covering tape and cotton were removed, and digit skin wrinkling was photographed and graded on visual inspection [Figure 1a] by two independent examiners and assigned a score on a grading scale of 0–4, as per a previously published grading scale[11,26] given below:

Grade 0: complete absence of wrinkling

Grade 1: just recognizable wrinkling (fingertip not completely smooth)

Grade 2: two or less lines of wrinkling on the fingertip

Grade 3: three or more lines of wrinkling on the fingertip

Grade 4: wrinkling completely distorting the pulp of the finger

Grades 3 and 4 were considered as normal.

The persons who graded the wrinkling were blind to the nerve conduction result. If different grades were assigned by the two persons, the average grade was taken for analysis.

Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (v16, IBM, Chicago, Illinois, US) software. The Kolmogorov–Smirnov test was used to test the data for normality. For non-parametric data, comparison between two groups was done using the Mann–Whitney test and multiple comparisons were done between the groups using the Kruskal–Wallis test. Parametric data were compared with the Student *t*-test. $P < 0.05$ was considered significant. A linear regression analysis was used to find the relationship between two continuous variables.

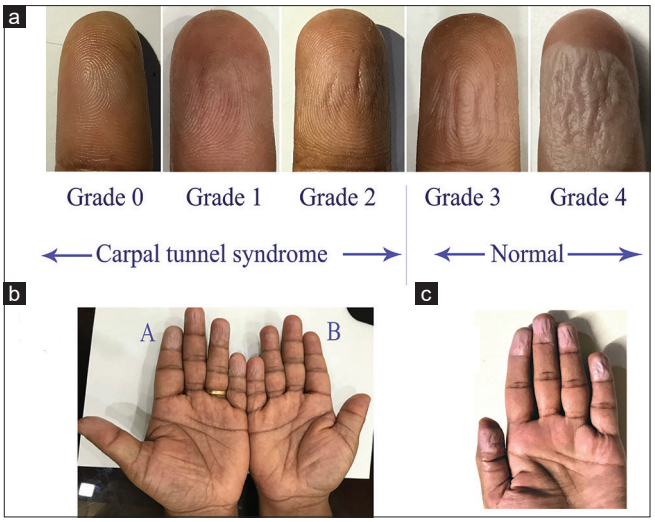

Figure 1: (a) EMLA-induced stimulated skin-wrinkling grades (grades 0–4). (b) Both hands of a patient showing the EMLA-induced stimulated skin-wrinkling test response: (A) left hand with negative test result and (B) right hand with positive test result with sparing of the fifth digit. (c) Control hand with normal EMLA-induced stimulated skin-wrinkling test response

Results

During the study period, 78 hands of 53 patients were clinically diagnosed with idiopathic CTS. Of whom, five symptomatic hands had very rough palm with callosities and were not included in the study. Twelve patients with clinically bilateral CTS and seven patients with unilateral CTS did not give consent for the study participation and hence not included. The remaining 42 hands of 31 patients clinically diagnosed with CTS were enrolled in this study. In 20 patients, the single affected or most affected hand and in 11 patients both affected hands were included. There were 7 males and 24 females with a mean age of 42.5 ± 7.1 years.

Thirty asymptomatic hands of 20 persons (6 males and 14 females) were enrolled as controls. This included both hands of 10 and dominant hands of 2 healthy volunteers and asymptomatic hands of 8 patients with unilateral CTS enrolled as cases. The mean age of controls was 42.8 ± 8.9 years.

There was a significant difference in the grade of SSW induced by EMLA cream between symptomatic and control hands (Mann–Whitney test, $P < 0.0001$) in all digits [Figure 1b and c]. Thirty five of 42 (83.3%) symptomatic hands showed EMLA positivity with a skin-wrinkling grade below 3 in the index finger with a sensitivity of 85.7% and specificity of 81.1%. Performing the EMLA test on all digits and taking the average skin-wrinkling grade of the lateral four digits (digits 1, 2, 3, and 4) yielded positive results in 38 out

of 42 (90.5%) symptomatic hands with a better sensitivity and specificity of 91.3% and 83.3%, respectively.

Table 1 gives a comparison of the sensitivity and specificity of EMLA testing with nerve conduction studies. In hands clinically diagnosed with CTS, NCS without comparison studies (Bland grade 2 or more) showed a sensitivity of 82.4% and specificity of 93.8%. However, with comparison studies, the sensitivity increased to 93.3%, but specificity was only 79%. Combining EMLA test with NCS and considering the positivity of any one of these tests yielded maximum sensitivity (97.7%) but specificity was much lower (71.4%). Among clinically asymptomatic control hands, NCS comparison studies showed false positivity of 26.7%, whereas EMLA testing of digit 2 showed false positivity of 23.3%.

Among symptomatic and asymptomatic hands, there was no significant difference in the wrinkling grades of lateral four digits at all grades of electrophysiological severity (Kruskal–Wallis test, $P > 0.05$). However, the fifth digit of symptomatic hands showed a higher wrinkling grade that was significant compared to that of digit 2 (Mann–Whitney test, $P = 0.005$) and the mean wrinkling grade of digits 1, 2, 3, and 4 (Mann–Whitney test, $P = 0.019$). Nevertheless, the fifth digit of 22 symptomatic hands showed a wrinkling grade in the positive range (<3). Disease severity assessed by EMLA test showed positive correlation with NCS severity grade [Table 2]. Linear regression analysis showed that the NCS grade was negatively correlated with EMLA wrinkling grades (grades 3 and 4 were taken as normal and grade 0 was taken as the most severely affected) for digit 1 (linear regression analysis, $r = -0.5508$, 95% confidence interval [CI] −0.5369 to − 0.1866, $r^2 = 0.3034$, $P = 0.0002$), digit 2 (linear regression analysis, $r = -0.5211$, 95% CI − 0.5964 to − 0.1866, $r^2 = 0.2715$, $P = 0.0004$), digit 3 (linear regression analysis, $r = -0.2728$, 95% CI − 0.3873 to − 0.02313, $r^2 = 0.07441$, $P = 0.0805$), digit 4 (linear regression analysis, $r = -0.2703$, 95% CI − 0.4008 to 0.02589, $r^2 = 0.07308$, $P = 0.0834$), and mean digit score (linear regression analysis, $r = -0.4548$, 95% CI − 0.5914 to − 0.1361, $r^2 = 0.2068$, $P = 0.0025$). Thus, patients with electrophysiologically advanced disease showed significantly stronger EMLA positivity (lower skin-wrinkling grades) when compared to those with electrophysiologically mild disease (higher wrinkling grade). Twenty of 21 hands (95.2%) with moderate or severe grades of NCS severity (Bland grade 3 and above) were EMLA positive.

A majority of the hands (30 of 42) reported extra median (glove) distribution of symptoms with the involvement of the medial one and half digits also [Table 2]. Of these 30 hands, the fifth digit showed EMLA positivity in 17 (56.7%) and negativity in 13 (43.3%) hands. The remaining 12 hands reported a median distribution of symptoms, but EMLA testing in them showed extra median involvement with involvement of the fifth finger in 5 (41.7%) hands; in 7 of 12 hands (58.3%), the fifth finger was EMLA negative (unaffected). Among control hands, there was no significant difference (Student's *t*-test, $P < 0.001$) in wrinkling grades between NCS-positive and NCS-negative hands [Table 2].

Table 3 shows the correlation of different clinical scores with EMLA and NCS results. The EMLA test showed a better correlation with symptom severity compared to NCS. Boston symptom severity scale (SSS) score and all domains of neuropathic pain score assessed with NPSI were significantly higher in EMLA-positive hands when compared to EMLA-negative symptomatic hands (Mann–Whitney test, $P = <0.025$). However, these symptom scores were not significantly different in NCS-positive and -negative hands (Mann–Whitney test, $P > 0.05$).

All affected hands reported tingling paresthesia and pins' and needles' sensations. Twenty five out of 35 EMLA-positive patients (71.4%) reported pain as a prominent symptom,

Table 1: Comparison of the 90-min extended EMLA test and nerve conduction study-sensitivity and specificity

	Positive hands (*n*)	Sensitivity	Specificity
Symptomatic hands (*n*=42)			
EMLA test-wrinkling grade digit 2-<3	35	85.7%	81.1%
EMLA test-mean wrinkling grade digit 1, 2, 3, and 4-<3	38	91.3%	83.3%
NCS standard	33	82.4%	93.8%
NCS with comparison studies	39	93.3%	79.0%
EMLA D2+NCS (standard)-either test positive	38	91.3%	79.0%
EMLA D2+NCS comparison studies-either test positive	41	97.7%	71.4%
EMLA D1, D2, D3, and D4 mean+NCS (standard)-either test positive	40	95.5%	81.1%
EMLA D1, D2, D3, and D4 mean+NCS comparison studies-either test positive	41	97.7%	71.4%
Control hands (*n*=30)	Negative hands		
EMLA test-wrinkling grade digit 2-≥3	23		
EMLA test-mean wrinkling grade digit 1, 2, 3, and 4-≥3	24		
NCS standard	28		
NCS with comparison studies	22		
EMLA D2 with NCS (standard)-both test negative	22		
EMLA D2 with NCS comparison studies-both test negative	18		

EMLA test: Eutectic mixture of local anesthetic test; NCS: nerve conduction study. D1, D2, D3, D4: Digit 1, 2, 3, and 4

whereas pain was present only for 2 out of 7 EMLA-negative hands (28.6%). More than 25% of EMLA-positive hands reported itching and burning pain as symptoms while none of the EMLA-negative hands reported these symptoms. Thirty four out of 35 patients (97.1%) with Boston SSS ≥ 23 (moderate, severe, and very severe symptoms[27]) showed EMLA positivity, but only 1 out of the 7 patients (14.3%) with mild symptoms (Boston SSS ≤ 22) recorded a positive EMLA test [Table 4].

Discussion

There have not been many studies on the clinical utility of EMLA in CTS diagnosis and those that exist were mostly conducted by Wilder-Smith and his team. In 2004, he assessed EMLA-induced vasomotor dysfunction in CTS by measuring blood flow velocity changes 30 min after the topical application of EMLA cream and demonstrated its usefulness in the diagnosis of CTS with sensitivity and specificity of 69% and

Table 2: Correlation of electrophysiological severity and symptom distribution with EMLA-stimulated skin-wrinkling grade

Hands with symptoms***	EMLA-stimulated skin-wrinkling grade							
	EMLA positive (n)	Digit 1 (*n*=31)	Digit 2 (*n*=35)	Digit 3 (*n*=31)	Digit 4 (*n*=32)	Mean digits 1, 2, 3, 4	Digit 5** (*n*=22)	*P**
NCS grade	All hands *n*=42	1.27 (1.23)	1.25 (1.12)	1.4 (1.21)	1.49 (1.16)	1.34 (1.01)	2.0 (1.23)	>0.05
	Grade 0/1 *n*=5/9[##]	2.61 (0.99)	2.17 (1.0)	1.72 (1.03)	2.0 (1.0)	2.07 (0.79)	2.44 (0.88)	>0.05
	Grade 2 *n*=9/12[##]	1.13 (1.25)	1.5 (1.0)	1.83 (1.19)	1.58 (0.996)	1.51 (1.0)	1.92 (1.16)	>0.05
	Grade ≥3 *n*=20/21[##]	0.79 (0.87)	0.71 (0.94)	1.02 (1.21)	1.21 (1.27)	0.93 (0.92)	1.86 (1.39)	>0.05
Symptom distribution	Median distribution	1.25 (1.06)	1.04 (1.096)	0.96 (1.05)	1.08 (1.16)	1.08 (0.97)	2.25 (1.29)	>0.05
	Extra median distribution	1.28 (1.30)	1.33 (1.13)	1.58 (1.23)	1.65 (1.14)	1.45 (1.02)	1.9 (1.21)	>0.05
Control hands***	All hands	2.97 (0.93)	3.17 (0.87)	3.37 (0.72)	3.30 (0.92)	3.22 (0.72)	3.3 (0.84)	>0.05
	NCS negative [#]*n*=22	2.95 (0.999)	3.23 (0.87)	3.36 (0.73)	3.23 (0.97)	3.31 (0.72)	3.14 (0.99)	>0.05
	NCS positive [#]*n*=8	3 (0.76)	3.0 (0.93)	3.375 (0.74)	3.375 (0.74)	3.5 (0.76)	3.5 (0.53)	>0.05

Data are expressed as mean with standard deviation in parenthesis. *Multiple intergroup comparisons of mean wrinkling grades of all digits, except digit 5, by Kruskal-Wallis test. **Comparison of the EMLA wrinkling grades of digit 2 and mean D1, 2, 3, and 4 with digit 5 by Mann-Whitney test showed *P* values 0.005 and 0.019, respectively. ***Comparison of symptomatic and control hands by Mann-Whitney test showed *P*<0.0001 for digits 1, 2, 3, 4, and 5. [#]Comparison of mean wrinkling grade of digits by Student's test, *P* value D1=0.908 D2=0.538, D3=0.970, D4=0.480, D5=0.335. [##]*n*=EMLA-positive hands among the total number

Table 3: Correlation of different clinical scores with EMLA and NCS results

	EMLA positive *n*=35	EMLA negative *n*=7	*P**	NCS positive *n*=33	NCS negative *n*=9	*P**
BCTQ SSS	34.43 (7.84)	18.86 (7.49)	<0.0001	34.43 (7.84)	28.33 (10.14)	0.232
NPSI						
Total	35.86 (17.07)	11.43 (13.05)	0.0012	35.86 (17.07)	27.33 (19.29)	0.412
Burning pain	1.74 (1.87)	0	0.009	1.74 (1.87)	0.67 (1.0)	0.147
Pressing pain	2.46 (1.92)	0.57 (1.51)	0.025	2.46 (1.92)	1.78 (2.17)	0.598
Paroxysmal pain	3.51 (1.84)	0.57 (1.51)	0.0004	3.51 (1.84)	2.22 (2.17)	0.207
Evoked pain	4 (2.63)	1.43 (2.3)	0.019	4 (2.63)	3.33 (2.92)	0.781
Paresthesia/Dysesthesia	6.49 (1.82)	3.14 (1.57)	<0.0001	6.49 (1.82)	5.67 (2.45)	0.846

EMLA positive: Eutectic mixture of local anesthetic test positive; NCS positive: standard nerve conduction study positive; BCTQ SSS: Boston Carpal Tunnel Questionnaire symptom severity subscale; NPSI: neuropathic pain severity inventory. Data are expressed as mean with standard deviation in parenthesis. *Mann-Whitney test

Table 4: Correlation of reported symptoms and BCTQ SSS grade with NCS and EMLA results

	EMLA positive *n*=35	EMLA negative *n*=7	NCS positive *n*=33	NCS negative *n*=9
Paresthesia/Dysesthesia	35 (100%)	7 (100%)	33 (100%)	9 (100%)
Pain	25 (71.4%)	2 (28.6%)	22 (66.7%)	5 (55.6%)
Burning sensation	10 (28.6%)	0	8 (24.2%)	2 (22.2%)
Itching	9 (25.7%)	0	8 (24.2%)	1 (11.1%)
BCTQ SSS Mild (12-22) *n*=7	1 (14.3%)	6 (85.7%)	4 (57.1%)	3 (42.9%)
BCTQ SSS Moderate (23-33) *n*=14	14 (100%)	0	11 (78.6%)	3 (21.4%)
BCTQ SSS Severe (34-44) *n*=16	15 (93.8%)	1 (6.2%)	13 (81.2%)	3 (18.8%)
BCTQ SSS Very severe (45-55) *n*=5	5 (100%)	0	5 (100%)	0

EMLA positive: Eutectic mixture of local anesthetic test positive; NCS positive: standard nerve conduction study positive; BCTQ SSS: Boston Carpal Tunnel Questionnaire symptom severity subscale. Data as actual number of hands and percentage in parenthesis

68%, respectively.[13] Triki *et al*.[14] compared the sensitivity and specificity of the EMLA test (30 min of topical application on digit 2 only) with that of NCS and sympathetic skin response in the diagnosis of CTS. They found a sensitivity of 69.4% and a specificity of 50% for the EMLA test with a good correlation of this test with clinical data. In comparison, NCS had a sensitivity of 66.7% and a specificity of 72.7% while SSR had a poor sensitivity of 22.2% but a high specificity of 90.9%. Either EMLA or NCS abnormalities (versus both tests being normal) increased sensitivity to 88.9% but decreased specificity to 45.4%.

In this study, we observed that visual inspection and grading of the EMLA-SSW in the index finger after 90 min of topical application aid in the diagnosis CTS with better sensitivity and specificity (85.7% and 81.1%, respectively). Topical application of EMLA on all digits and taking the mean wrinkling grade significantly increased sensitivity to 91.3%. Diagnostic efficiency of this extended EMLA test was found to be 83.4% for the digit 2 and 87.3% for the mean (digits 1, 2, 3, and 4) (for EMLA test digit 2, Likelihood ratio (LR) + =4.53 and LR− =0.17; for EMLA test mean (digits 1, 2, 3, and 4), LR+ =5.40, and LR− =0.10), whereas the diagnostic efficiency of NCS was 88.1% for the standard and 86.15% for comparison studies (NCS standard: LR+ =13.21 and LR− =0.18; NCS comparison studies: LR + =4.44 and LR− =0.08). Combining EMLA with NCS and considering the positivity of any one of these tests yielded the highest sensitivity (up to 97.6%), but its specificity was much lower (71.4%). It may be noted that most of our control persons were housewives and manual workers who were regularly engaged in hand-intensive work which is known to be a risk factor for CTS.[28] It is possible that many of them had work-related subclinical large-fiber dysfunction without any symptoms. This may be a reason for the high false-positivity rate (26.7%) for sensitive NCS comparison methods among asymptomatic hands.

Padua *et al*.[29] observed that hands with negative or minimal electrophysiological changes had higher symptoms than those with significant NCS abnormalities. Similar clinical and electrophysiological dissociation was also reported by many other previous authors.[2,3] In our study, the EMLA test showed better correlation with symptom severity than NCS. Moreover, in patients with more intense symptoms, sensitivity of the EMLA test appeared to be superior to that of NCS comparison studies. However, in minimally symptomatic electrophysiologically mild CTS, the EMLA test was less sensitive. This study also shows that most of the pleomorphic symptomatology of CTS is at least partly and, in many cases, exclusively mediated by small fibers and these fibers are prominently affected in most patients with CTS. Tamburin *et al*.[5] noticed that small-fiber damage takes place earlier than large-fiber dysfunction in CTS and also observed that daytime pain and symptom severity assessed by Boston SSS were significantly correlated with Aδ-fiber damage. Schmid *et al*.[30] proved prominent small-fiber damage in compressive neuropathies like CTS through quantitative sensory testing (QST) and the measurement of the density of IENFD and found that this small-fiber involvement is independent of the electrophysiologically detectable large-fiber involvement.

Similarly, in this study, EMLA test grades showed a positive correlation with NCS severity grades indicating that small-fiber involvement in CTS almost parallels large-fiber damage. Further, in hands with electrophysiologically advanced disease, the EMLA test showed positivity in all except one hand. This demonstrates the clinical utility of the EMLA test not only for those symptomatic patients with negative or minimal electrophysiological abnormalities but also for those with electrophysiologically advanced disease irrespective of their symptoms. In those patients with significant small-fiber damage, recovery after surgical release may require significant axon regeneration/collateral sprouting to restore cutaneous innervation to normal levels.[30] Thus, stronger EMLA positivity may predict delayed and incomplete symptom resolution after surgical release.

More than 50% of the symptomatic hands in this study showed sympathetically mediated vasomotor dysfunction of the fifth digit also. Zanette *et al*.[31] analyzed extra median sensory impairment with QST and found fifth digit involvement in 33.3% of hands and postulated central sensitization as the mechanism for this extra median pattern of sensory impairment. It is also possible that there is a significant overlap in the sympathetic distribution of the hand and sympathetic nerves may not follow the conventional somatic fiber pattern. This may also be a reason for the commonly observed pattern of extra median symptom distribution involving the fifth digit. Wilder-Smith *et al*.[13] also reported mild insignificant reduction in the vasomotor function of the fifth digits in CTS hands. Many other researchers have described substantial variability and overlap in the sympathetic innervation of the hand.[32,33] It is also possible that the ulnar nerve carries a lower number of sympathetic fibers as compared to the median nerve and thus the little finger might be getting less sympathetic innervation with resultant decreased vasoconstriction.[34]

Reduced SSW has been used as a diagnostic test of limb sympathetic nerve function in leprosy,[35] diabetic neuropathy,[26] idiopathic small-fiber neuropathy,[36] and for screening for HIV neuropathy[37] and found to closely correlate with IENFD in diagnosing small-fiber neuropathy.[12] EMLA-induced SSW shows a more linear response than water-induced wrinkling[25] and is found to have good reproducibility and interobserver agreement.[11,12]

Previous studies[14] found fairly high sensitivity for a 30-min EMLA test with much lower specificity, limiting its diagnostic utility in CTS. However, in our study, extending the duration of topical application of EMLA (90 min) significantly improved both sensitivity and specificity and probably has the potential of being used complementary to NCS or even as an alternative to electrophysiological studies in general practice settings.

Limitations

First, the number of patients included in this study was limited. Further, we excluded several hands with callosities and rough palm skin. Persons over 55 years were also not included in the study as the natural wrinkling in their palms might have made the interpretation of the wrinkling grade difficult. Many manual workers and housewives may have callosities in their digits and the suitability of EMLA in such hands is uncertain. However, the option of comparing the area of stimulated wrinkling with that of the adjacent control skin may be considered in these types of situations.[12] As patients have to come back for the test another day and have to stay in the outpatient department for nearly 2 h, many patients with minimal symptoms did not agree to be included in the study. Hence, a case selection bias with the possibility of more symptomatic patients being included in this study cannot be ignored.

Conclusion

The EMLA test, which assesses the small unmyelinated C fibers mediating sympathetic vasomotor function, showed better correlation with symptom severity than NCS. This test is particularly useful in those symptomatic patients with normal NCS, as these patients might have exclusive small-fiber involvement in the early stages of the disease. Among severely symptomatic CTS patients, the EMLA test showed sensitivity higher than NCS and this test may be considered as a better alternative for NCS. Moreover, stronger EMLA positivity suggests severe small-fiber involvement and thus may predict poor and delayed symptom resolution after surgical release. It is important to note that, unlike NCS, the EMLA test is very inexpensive, easy to perform at bedside or in the OPD and does not require a neurophysiology lab or the services of a neurotechnologist. Hence, it is worth studying this test in a large heterogeneous group of patients having varying symptoms and electrophysiological severities to assess its potential utility in routine clinical practice, especially in low-resource general practice settings.

Acknowledgments

The authors acknowledge the help of Dr. Ajith TA, Professor of Biochemistry and staff of Neurophysiology Laboratory, Amala Institute of Medical Sciences, Amala Nagar, Thrissur, India during the study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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