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Research paper

The value of ultrasound-guidance of nerves and muscles for patient tolerance and parameters electrodiagnostic studies

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ABSTRACT

Objective: To assess impact of ultrasound guidance (USG) on patient's perception of nerve conduction studies (NCS).
Methods: In this single-center, randomized, sham-controlled, parallel, single-blind trial, we evaluated ultrasound (US) in identifying NCS stimulation site. Consecutive adults (18–80 old) without neuropathy referred for NCS were electronically randomized 1:1 to USG or Sham US. The primary outcome was sensory supramaximal intensity (SSMI) for each site/nerve; motor supramaximal intensity (MSMI), amplitudes, number of non-routine muscle punctured, Visual Analogue Scale (VAS), satisfaction were secondary outcomes.
Results: 290 participants were randomized, with 145 in the USG and 144 Sham US groups, respectively. No difference in SSMI, CMAP or SNAP, VAS, satisfaction was recorded. With USG, the median at the elbow and fibular MMSI were lower ($p = 0.04$; $p = 0.02$). With normal NCS or overweight and obese subgroups patients had lower median SSMI ($p = 0.05$/ $p = 0.02$), higher median and sural SNAP with normal NCS ($p = 0.04$; $p = 0.007$) and the sural SNAP for the expert US subgroup ($p = 0.02$).
Conclusions: USG is useful for nerves, that are anatomically variable or in obesity. The sural SNAP gain with US in the normal NCS subgroup could facilitate routine NCS.
Significance: In standard NCS the USG does not modify the patient's tolerance.
Trial Registration: clinicaltrials.gov (NCT03868189).

1. Introduction

Ultrasound (US) is increasingly used in neuromuscular pathologies for diagnosis and follow-up (Herraets et al., 2020; Padua et al., 2012; Rattay et al., 2017; Telleman et al., 2018). In routine practice, US is used for local anaesthetic nerve block (Helen et al., 2015) and for the injection of botulinum toxin (Kaymak et al., 2018). More recently, US has demonstrated effectiveness for guidance in sensory nerve studies to place electrodes or locate the optimal stimulation site (Boon et al., 2011a; Cartwright et al., 2019; Choi et al., 2019; Deimel et al., 2013; Evangelopoulos et al., 2017; Kamm et al., 2009; Kim et al., 2017; Park et al., 2015; Scheidegger et al., 2016, 2011; Wei et al., 2021). Amplitude responses could be higher and supramaximal intensity (SMI) lower in healthy volunteers (Cartwright et al., 2019; Choi et al., 2019; Kamm et al., 2009; Kim et al., 2017; Park et al., 2015; Scheidegger et al., 2016, 2011; Wei et al., 2021).

In nerve conduction studies (NCS), electrical stimulation can cause discomfort. Age, sex and BMI do not seem to influence pain sensation (Strommen and Daube, 2001; Wee et al., 2004). NCS are commonly performed with surface electrodes, positioned using anatomical landmarks. US nerve tracking could identify the optimal stimulation site (locating the shallowest nerve site) to obtain the maximum amplitude response with minimal current intensity, although there has been little research into the clinical benefit of this technique.

Abbreviations: BMI, Body mass index; CTS, Carpal tunnel syndrome; CMAP, Compound muscle action potential; EMG, Electromyography; GLMM, General linear mixed model; MSMI, Motor supramaximal intensity; NCS, Nerve conduction studies; NSS, Neuropathy Symptom Score; SSMI, Sensitive supramaximal intensity; SNAP, Sensory nerve action potential; SMI, Supramaximal intensity; US, Ultrasound; USG, Ultrasound guidance; VAS, Visual Analogue Scale.

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We hypothesized that US-tracking to identify the optimal stimulation nerve site could reduce the intensities delivered to the patient and thus improve compliance and tolerance. The main objective of this study was therefore to compare the SMI delivered to the sensory nerves in each usual site during a standard NCS in two groups: an interventional group with US-guided optimal stimulation nerve site, and a control group (Sham US). The secondary objectives were to compare the motor supramaximal intensity (MSMI), sensory nerve action potential (SNAP), compound muscle action potential (CMAP) and the choice of muscles explored between groups. We also evaluated the examination duration, the patient's satisfaction, and pain sensation. Subgroup analysis compared several evaluation criteria according to US expertise, verifying the feasibility by non-expert physicians and normal versus abnormal NCS, to ensure that results are not biased by axonal loss. The aim was to determine whether this strategy was feasible in practice and not too time-consuming. We chose to assess our current practices in patients who presented with radicular or entrapment pathology. We excluded patients with neuropathy or with pathologies linked to neuropathy to have a homogeneous and comparable population in the two groups. We wanted to know if the use of the ultrasound machine modified the choice of muscles explored and in particular if more non-routine muscles were explored with the comfort and security of visual ultrasound control.

2. Methods

2.1. Study design and participants

This was a single-center, randomized, single-blind, placebo-controlled, parallel trial. Adult inpatients (18–80 years) were eligible if they had been referred to the CHU Nîmes for NCS which allowed the application of a standard examination protocol. They were ineligible if they presented symptoms of neuropathy on examination, an NSS (Neuropathy Symptom Score) score ≥ 3, an abnormal clinical examination or antecedent metabolic diagnosis like diabetes mellitus or renal failure. Pregnant, parturient, or breastfeeding patients were also excluded.

2.2. Standard protocol approvals, registrations, and patient consents

Patients gave written informed consent prior to data collection. The trial was approved by the CPP Sud Ouest et Outremer 1 (RCB# 2018-AO2872-53) and the protocol was registered on clinicaltrials.gov (NCT03868189).

2.3. Intervention

For the intervention group, motor and sensory nerves were located by US prior to NCS and the most superficial nerve location (optimal stimulation site) was marked on the skin. US tracking was performed with a portable ultrasound system, Samsung HM70A and a high-frequency linear probe LA3-16AD. The sites for stimulation were marked with a marker pen. First, the nerves were identified in the axial section using a scan from top to bottom (elevator technique to localize a nerve and following it proximally or distally). The median and ulnar nerves were identified at the wrist and elbow. The radial nerve sensory branch was marked on the forearm. We located the fibular and tibial nerves at the ankle and the neck of the fibula or the popliteal fossa. The most superficial location of the sural nerve and the superficial fibular nerve were also marked.

For the control group, a sham US guidance was used, with a frozen image not visible to the patient and non-ultrasound guided skin marking preceding NCS. Stimulations were performed on the median, ulnar, and fibular nerves at 8 cm from the active electrode, and on the tibial nerve at 12 cm.The sensory median and ulnar nerves were stimulated at the wrist and recorded respectively at the third and fifth fingers. The superficial radial nerve was stimulated on the radial edge at the forearm lower third and recorded at the anatomical snuffbox at 12-cm proximal to the active electrode. The sural nerve was stimulated at the mid-calf at 14-cm proximal to recording electrode and recorded at the external malleolus. The superficial fibular nerve was stimulated at the lower third anterolateral face at 12-cm proximal to the active electrode and recorded at the front of the ankle.

All muscles were punctured under simulated US guidance. The muscle was identified by the passive or active movement in an US axial section. Vascular damageable structures were recognized.

Muscles were classified as "routine" (those routinely explored such as the tibialis anterior, 1st dorsal interosseous muscle) or "non-routine" (those not performed routinely because of their depth or vascular proximity (i.e. the tibialis posterior muscle, pronator teres) according to the experience in this center. We thus defined 16 usual muscles comprising six lower limb and 10 upper limb muscles (Supplementary Table A.1).

2.4. Outcomes

The primary outcome was to compare the SSMI delivered during a standard NCS between the two groups. The secondary outcomes were to compare the motor supramaximal intensity (MSMI), SNAP, and CMAP for each nerve or stimulation site and the total number of muscles explored. We also compared the number of non-routine muscles, overall examination time (between the beginning of the first nerve stimulation and the end of EMG), and average time per explored site (overall time divided by the number of nerves and muscles explored). Finally, patients rated the tolerability of the exam on a Likert scale (intolerable, difficult to tolerate, tolerable or painless), their satisfaction (not at all satisfied, slightly satisfied, good, or excellent) and pain felt on a 0–100 visual analogue scale (VAS). We also planned a subgroup analysis of measurements according to the level of expertise of the physician. An auxiliary exploratory subgroup analysis comparing normal and abnormal examinations was added because pathology may alter the measurements.

2.5. NCS and EMG protocol

Features were recorded using a Dantec Keypoint G4 Workstation (Natus France, Merignac, France) with pre-gelled disposable surface electrodes (Natus) and a signal bandpass filtering Hz of 1 kHz to 10 kHz. Patient skin was warmed to 32 °C if necessary. Indication for NCS, sex, age, weight and height were noted. A pre-established standardized stimulation protocol was used to homogenize the physicians' practices. For the motor nerves, the stimulation duration of the rectangular pulse was 0.5 ms, except at the popliteal stage for the tibial nerve, where the duration was 1 ms. In the lower limbs, the initial intensity was 20 mA at the ankle and neck of the fibula, and 50 mA for the tibial nerve at the popliteal fossa. On the upper limbs, the initial intensity was 15 mA on the wrist and elbow, then the intensity increased to 3 to 5 mA until the maximal response. For the sensory nerves, stimulation intensity was gradually increased until visually obtaining the maximum SNAP and was averaged by 10 stimulations. The stimulation duration was 0.3 ms using a frequency of 3 Hz. All sensory NCS were performed antidromically. For the EMG, the muscle choice was at the physician's discretion depending on the clinical question and his desire for choice non -routine muscle or not.

2.6. Investig ators

Three physicians trained in NCS participated in this trial. One had four years' experience in US practice (expert), one had practiced US-guided botulinum toxin (intermediate), and the other had never used US (beginner). The two non-experts received two hours of training in US acquisition with the expert and three half-days of US manipulation alone.

2.7. Sample size

The few published data on NCS stimulation intensities (Cartwright et al., 2019; Nashed et al., 2009; Wei et al., 2021) use different intensities to those delivered in our current practice, and thus could not be used to calculate the sample size. We therefore performed a preliminary study. The SMI were recorded in 30 consecutive patients for standard NCS. The stimulation duration was 0.3 ms using a frequency of 3 Hz. For the sensory nerves, stimulation intensity was gradually increased until visually obtaining the maximum SNAP and was averaged by 10 stimulations. The results found SSMI of 11.6 (±3.9) mA in the upper limbs, and 13.9 (±4.5) mA in the lower limbs, with intra-class correlation coefficients respectively at 0.45 [0.30–0.60] and 0.62 [0.45–0.77]. Using the worst values of these data, with between 2 and 10 measurements expected per patient and setting a target for reducing the SSMI at 3 mA (minimum difference perceptible by a patient), 118 patients would be necessary (with 5 % alpha risk and 90 % power). To consider of the different effect levels to be estimated, this number was increased by 45 % (assumption on the distribution of patients who would have an exploration of the upper and lower limbs), plus a 10 % margin for any missing or unusable data. Thus, the sample size was set at 290 patients to be included over a one-year inclusion period.

2.8. Randomization and blinding

Participants were randomly assigned (1:1) via a central computer-generated randomization list after checking the eligibility criteria and before the examination. A block randomization list was established, stratified by age and nerve location, centrally from the CHU de Nîmes by the methodologist using a specifically designed SAS (Cary, NC, USA) program. For each combination of age group (18–40 years / 41–60 years / 61–80 years) and each location of NCS (upper limbs, lower limbs, upper and lower limbs), this stratified randomization gave nine strata. Only the methodologist knew the number of subjects per block size of 2 or 4. The trial was a single-blind study; with patients unaware of their group. In the control group, US guidance was simulated. The statistical analysis was carried out blinded to patient arm.

2.9. Data analysis

Statistical analysis was made using SAS (9.4; SAS Inc., Cary, NC, USA). The intention-to-treat analyses included all patients, except those that refused the test.

All statistical tests were conducted as 0.05 two-sided tests.

Results were expressed with mean, (SD) or median [25-75IQ] according to distribution. The numbers and associated percentages were given for categorical variables. Comparisons of MSMI, SSMI, SNAP and CMAP were made using a general linear mixed effects model (GLMM) with repetitions factor (all measure points left or right and nerve location) and a group factor (USG versus Sham US). To evaluate whether group effect differed by nerve location, the interaction term between nerves and group was also tested. When interaction term was significant, comparisons of MSMI, SSMI, SNAP and CMAP were made by nerve using a Student *t*-test or Wilcoxon-Mann-Whitney test with Hochberg significance level correction of statistical test. These tests were performed in complement to the general linear mixed model in all cases. A subgroup analysis was added to test the effect of BMI (obese/overweight).

3. Results

3.1. Participant flow

Between 4th April 2019 and 28th January 2020, 290 participants were recruited in Nîmes CHU neurophysiological laboratory and were randomly assigned to Sham US (n = 145) or USG (n = 145) (Supplementary Figure A.1). Three participants with historical neuropathy and/or abnormal neurological examination were erroneously recruited. One participant (Sham US group) refused the test due to pain and so could not be included in the analysis as no data were recorded. One other participant (Sham US group) lost consciousness during the exam, but had enough data for analysis of the primary outcome. Thus, 289 participants were included in the intention-to-treat analysis on the primary outcome.

Baseline characteristics were similar between the two groups (Table 1). Patients were predominantly female (61 %), with an average age of 51 ± 14 years and average BMI of 26 ± 5 kg/m2. Seventy five (26 %) patients scored 1 on the NSS, and 68 (23 %) scored 2. The most frequent investigation was of the upper limbs (69 %), followed by the lower limbs (28 %), with only 3 % for all four limbs.

In 162 cases (56 %), NCS results were abnormal. The most common final diagnoses retained were carpal tunnel syndrome (CTS) (n = 105), lumbar radiculopathy (n = 28). The distribution of CTS was not different (p = 0.68) between the two groups. As these pathologies lead to amplitude decrease, their distribution was verified to determine whether additional analyses needed to be performed.

A median of four sensory nerves were explored per patient (range 0 to 10). The median number of motor nerves explored per patient was 8, with a range of 0 to 16. One patient had no nerve exploration because the examination was stopped prematurely due to pain. An EMG was performed in 98 % of cases (100 % in the USG group and 97 % in the Sham US group). During EMG, 107 (38 %) patients had a puncture of "non-routine" muscles, with a median of 2 [1; 2]. (List of all nerves stimulated and muscles punctured: Supplementary Table A.2.).

Table 1
Patient characteristics.

Patient characteristics	USG group (N = 145)	Sham US group (N = 145)	P values
Female	93 (64.1 %)	83 (57.2 %)	0.2293
Age (years)	51 ± 14 (18; 80)	52 ± 14 (18; 79)	0.7418
BMI (kg/m^2)	25.64 ± 4.71 (16.38; 38.58)	26.32 ± 4.88 (17.23; 41.91)	0.2284
NSS 1 or 2	73 (50.3 %)	70 (48.3 %)	0.7246
Abnormal NCS results	82 (57 %)	80 (56 %)	0.8645
Carpal tunnel syndrome	51 (35 %)	54 (37 %)	0.6808
Lumbar radiculopathy	13 (9 %)	15 (10 %)	0.6767
Another nerve damage	19 (13 %)	10 (7 %)	0.0814

Quantitative data are expressed as mean ± sd or median [25-75IQ], and (range). Qualitative data are expressed as number (%).

Table 2
Sensory and nerve results: mean (sd) or median [25-75IQ] values by nerve the two groups on the intensity or amplitude.

SENSORY NERVES	Intensity (mA)			Amplitude (μV)		
	USG group	***Sham US group***	**p-value**	***USG group***	***Sham US group***	**p-value**
Median	*9.5 (3)*	*10.3 (4)*	0.11	*28.1 (17.4)*	*25 (16.3)*	0.23
Ulnar	*9 (3.5)*	*9.1 (3.6)*	0.70	*25 (14.1)*	*23.8 (14)*	0.40
Radial	*9.3 (2.5)*	*9.4 (3.2)*	0.70	*28.8 (13.3)*	*30.6 (13.5)*	0.40
Fibular	*12.7 (3.3)*	*13.5 (4.6)*	0.48	8.9 (5.8)	*7.4 (4)*	0.23
Sural	*11.9 (4)*	*12.9 (5.1)*	0.48	*9.8 (6.9)*	*8.2 (5.2)*	0.23
MOTOR NERVES	**Intensity (mA)**			**Amplitude (mV)**		
By nerve						
Median	20.1 *[17.1; 25.6]*	21 *[18; 27.6]*	0.11	*9.3 (3.2)*	*9.6 (3.2)*	0.47
Ulnar	18.4 *[15.1; 22.6]*	18.4 *[15.2; 22.8]*	0.8	*9.7 (2.5)*	*10.1 (2.4)*	0.13
By site						
Median (wrist)	20.2 *[18; 24.2]*	20.2 *[17.4; 25.2]*	0.97	*9.5 (3.2)*	*9.7 (3.2)*	0.95
Median (elbow)	20.1 *[15.4; 28.8]*	22.2 *[18.1; 30.8]*	0.04*	*9.1 (3.2)*	*9.5 (3.2)*	0.95
Ulnar (wrist)	18.5 *[15.4; 22.6]*	18.5 *[15.1; 22]*	0.97	*10.1 (2.5)*	*10.5 (2.4)*	0.95
Ulnar (elbow)	18.2 *[15; 22.4]*	18.3 *[15.3; 24.2]*	0.94	*9.4 (2.5)*	*9.7 (2.4)*	0.95
By nerve						
Fibular	23.8 *[20; 30.4]*	26.4 *[20.6; 36.1]*	0.02*	*5.4 (2.9)*	*5.6 (2.9)*	0.89
Tibial	50 *[29.2; 56]*	50 *[29.2; 59.4]*	0.82	*8.8 (5.3)*	*8.7 (4.8)*	0.89
By site						
Fibular (ankle)	24 *[20*; 33.6]	26.6 *[23.4*; 39]	0.02*	*5.6 (3.1)*	*5.8 (3)*	0.95
Fibular (neck)	23.4 *[20*; 29.6]	25.5 *[20.4*; 35.4]	0.39	*5.2 (2.7)*	*5.3 (2.7)*	0.95
Tibial (ankle)	29.4 *[24.4*; 38]	29.3 *[23.8*; 37.6]	0.96	*9.8 (5.6)*	*9.8 (4.8)*	0.95
Tibial (popliteal)	55.6 *[50.2; 62.2]*	57.8 *[50.4; 69.4]*	0.58	*7.8 (4.8)*	*7.7 (4.5)*	0.95

95 %CI = 95 % Confidence Interval, Shift difference are Hodges-Lehman estimates, * $p < 0.05$, significance.

Table 3
Comparison between US guidance group and Sham US group on examination time, muscle choice, pain and satisfaction.

	USG Group	Sham US Group	p-value
"Non-routine" muscles punctured	64 (44 %)	43 (31 %)	
Number of "routine" muscles	5 [4; 7] (1; 19)	5 [4; 7] (1; 17)	0.6000
Number of "non-routine**" muscles**	0 [0; 2] (0; 5)	0 [0; 1] (0; 3)	0.0024
Overall examination time, min	30 [26; 36] (12;78)	25 [20; 31] (3; 79)	<0.0001
Examination time per site, min	1.55 [1.35; 1.87] (0.72; 3.44)	1.33 [1.12; 1.61] (0.73; 3.76)	<0.0001
Pain rating (VAS)	28 [15; 45] (0; 87)	30 [16; 48] (0; 100)	0.3781
Good or excellent satisfaction	143 (99 %)	143 (99 %)	1
Tolerable or painless exam	141 (97 %)	134 (93 %)	0.0975

Quantitative data are expressed as median [25-75IQ], and (range). Qualitative data are expressed as number (%).

USG was performed in 68 patients (47 %) by an expert practitioner, 38 (26 %) by an intermediate practitioner and 39 (27 %) by a beginner practitioner.

3.2. Intensity, amplitude, nerve or site effects (Table 2)

SSMI between the USG and Sham US group was not different, regardless of the nerve studied.

A lower MSMI was delivered only to the median nerve on the elbow for USG group compared to Sham US group: −2mA [95 % CI −3.2; −0.2] (p = 0.04). However, by nerve, the MSMI of upper limb nerves in the USG group appeared to be lower than those in the Sham US group: *upper limbs:* β = -0.03 [95 % CI −0.09; 0.03] (p = 0.03). Only the fibular nerve revealed a lower MSMI delivered for USG group compared to Sham US group: −2.2 mA [95 % CI −4.2; −0.2] (p = 0.02). The SNAP and CMAP were not significantly different between the two groups. A nerve or site of stimulation effect was often observed with intensity delivered different depending on the site or nerve stimulated.

3.3. Muscular puncture and pain (Table 3)

Non-routine muscle puncture was more often performed when the practitioners used US (n = 64 (44 %)) than without (n = 43 (31 %)). With US, practitioners more often punctured pronator teres and psoas muscle (40 versus 1, and 21 versus 13, respectively) (Supplementary Table A.3). The overall examination time and time per muscle were longer in the USG group than the Sham US group: +5 min [95 % CI 3; 7] total, +0.21 min [-0.13; −0.30] per site explored (p < 0.0001). Median VAS pain assessment was 29 [16; 46], with no significant difference between the two groups (USG - Sham US: −2 [95 % CI −7; 3] p = 0.34). Most patients (95 %) rated the examination as tolerable or painless. Examination discomfort was not different between the two groups (p = 0.10). Patients were overwhelmingly satisfied (good or excellent) (99 %), with no difference between the two groups (p = 1).

3.4. Subgroup analysis: Normal or abnormal NCS (Supplementary Figure A.2)

Lower SSMI was delivered to the median nerve for the USG group compared to the Sham group: (USG - Sham US) = -1.3 mA [95 % CI −2.3; −0.3] for normal NCS (p = 0.05). For the other cases, regardless of the diagnosis, the tests did not reveal any significant difference in the SSMI delivered between the two groups. For normal NCS, the SNAP measured at the level of the median and sural nerves, was higher for the USG group than in the Sham US group: (USG - Sham US = +6.4 μV [95 % CI 1.5; 11.3]; normal NCS group 13.0 μV for USG, 9.0 μV for Sham US; p = 0.04) and + 4.0 μV [95 % CI 1.6; 6.4] 32.8 μV for Sham US; 39.3 μV for USG, p = 0.01). More non-routine muscles were explored for USG group (0 [0; 2]) than Sham US group (0 [0; 1]) only for the abnormal NCS (p = 0.003).

A longer examination time was observed for the USG group of 32 [27; 38] min compared to the Sham US group: 25 [20; 31] min, only for abnormal NCS ($p < 0.0001$). For normal diagnosis, the exam time was 27 [25; 31] min for USG group and 25 [20; 32] min for Sham US group ($p = 0.11$).

3.5. Subgroup analysis: Expertise level (Supplementary Figure A.3)

No difference in SSMI was seen between the two groups in univariate or multivariate model, whatever the practitioner expertise level or the nerve stimulated.

The US expert practitioner used lower MSMI in USG than in Sham US for lower limb, $\beta = -0.15$ [95 % CI −0.28; −0.03] ($p = 0.01$). There was not the case for the other two levels of expertise.

In the expert group on the sural nerve, a higher SNAP was recorded in USG group than in Sham US group (difference USG - Sham US: +2.6 μV [95 % CI 0.9; 4.4] ($p = 0.02$). Out of 110 measurements on the sural nerve by experts, 70 had a normal NCS and 40 an abnormal NCS. Separating normal and abnormal NCS, an effect was found only in the normal group: difference USG -Sham US: +4.6 μV [2.2; 6.9] $p = 0.002$ and not in the abnormal group: +1.1 μV [-0.9; 3.0] $p = 0.85$. The difference was not significant in the other expertise subgroups on the other sites. Whatever the expertise level and the nerve site explored, the CMAP were not different between the two groups. For CMAP or SNAP, no group effect was found according to the level of expertise.

The US expert opted to puncture more non-routine muscles in USG group (+2 [0–2]) than in Sham US group (0 [0–1]), ($p < 0.0001$). The choice to puncture non-routine muscles did not differ between US intermediates or beginners between the two groups.

3.6. Subgroup analysis: BMI (Supplementary Figure A.4)

A complementary analysis was performed to determine whether there was a difference in US guidance in obese or overweight patients. A difference was found only in SSMI, with overweight individuals on median and ulnar nerve, and with obese individuals on median nerve, and in MSMI with obese individuals on median nerve (wrist) (see Supplementary Figure A.4). Obese individuals had better amplitude with US on ulnar motor at wrist and elbow, but better amplitude with sham US on radial nerve.

4. Discussion

This large trial included 290 consecutive patients referred for NCS. We aimed to determine whether nerve detection via US could reduce the SMI and improve the SNAP or CMAP. The study focused on the SMI and not on the amplitude, which is more frequently studied (Cartwright et al., 2019; Frigeni et al., 2012; Kamm et al., 2009; Kim et al., 2017; Scheidegger et al., 2016, 2011), to establish if US guidance could reduce intensity and the discomfort arising from electrical impulses. Previous studies on intensity were in healthy volunteers (Cartwright et al., 2019; Wei et al., 2021). We chose to work in patients with radicular or entrapment pathology to discover the utility of US in current practice. Our trial was the first large randomized single-blind placebo-controlled study evaluating US in standard NCS with an all-comers design. The previous studies were in small or medium sized cohorts, ranging from 4 to 44 participants (Cartwright et al., 2019; Kamm et al., 2009; Kim et al., 2017; Wei et al., 2021).

The SSMI and MMSI did not differ significantly for most nerves, whatever the US experience level. The only significant difference comparing normal versus abnormal NCS subgroups was seen in the normal group for a lower median SSMI (USG 8.2 mA (2.7) / Sham US 9.6 mA (3.75) / $p = 0.05$) and on the median nerve MMSI at the elbow and on the fibular nerve (-2mA*0.5 ms, −2.2 mA*0.5 ms, respectively). However, these differences would need to be more extreme to be detectable to the patient. Cartwright et al. and Wei et al. showed a lower intensity with US (10–15 mA and −10.23–5.18 mA*ms respectively), the difference was perceived by participants (Cartwright et al., 2019; Wei et al., 2021).

In the literature, higher amplitudes after US tracking have been seen on certain nerves such as the sural, fibular superficial, saphenous and the lateral femoral cutaneous nerves (Deimel et al., 2013; Evangelopoulos et al., 2017; Kamm et al., 2009; Kim et al., 2017; Park et al., 2015; Scheidegger et al., 2016). These studies cannot be directly compared to ours because of the use of needle electrodes recording (Kamm et al., 2009) or comparing USG needle recording to NUG surface electrode recording (Deimel et al., 2013; Evangelopoulos et al., 2017; Kamm et al., 2009; Scheidegger et al., 2016, 2011). We chose not to modify our practices and to use electrodes. Recording by surface electrodes is less dependent on the position variation than with needle electrodes (Scheidegger et al., 2016; Ven et al., 2008). This may explain why it is more difficult to highlight a difference. Indeed, other studies like ours using a USG stimulus site and recording surface electrodes showed contrasting results. For the sural nerve, one trial found no difference in SNAP, but a lower SSMI (Cartwright et al., 2019). Another study found better SNAP (Choi et al., 2019), and for motor ulnar nerve, motor radial nerve, fibular superficial or lateral femoral cutaneous nerve, some studies found a better amplitude (Kim et al., 2017; Park et al., 2015; Wei et al., 2021). Sometimes the differences in absolute values were significant but very moderate (Park et al., 2015; Wei et al., 2021), which does not modify the final interpretation. In our study, the difference could shift the interpretation from normal to abnormal only for the sural nerve (normal NCS group 13.0 μV for USG, 9.0 μV for Sham US). Thus, USG could be useful in difficult situations, for example when the SNAP is not recorded or is lower than clinically expected by standard NUG techniques to confirm the SNAP value is not a technical error (Boon et al., 2011a; Kim et al., 2017). The disparities in stimulation techniques (duration, intensity) can limit comparability of studies (Cartwright et al., 2019; Choi et al., 2019). An amplitude/intensity ratio could have shown the benefit of US and the optimisation the intensity of stimulation. In this sense, for all sensory nerves except the radial nerve, we tended to stimulate less in the USG group for higher SNAP.

Nerve conduction velocity and amplitude decrease with obesity and age (Buschbacher, 1998; Chen et al., 2016; Nandedkar et al., 2021; Rivner et al., 2001). As obesity increases the nerve depth, the stimulus should increase. In our study, the BMI and age distribution in the two groups was similar. A stratification according to the BMI was performed and showed a benefit on median SSMI, on median MSMI at wrist, ulnar at wrist and elbow, where the location facilitates identification of where the nerve is the most superficial. The variability makes it difficult to demonstrate a significant difference in the lower limbs. The worse SNAP on the fibular nerve in the overweight and obese groups, and the better SNAP in the group without US for the radial nerve, probably arise from the difficulty in locating small sensory nerves in overweight or obese patients.

The examiners were all experienced in NCS with good knowledge of nerve anatomy. In standard NCS, the variability of most stimulation sites was low. These two elements could explain the lack of difference in our study. When an anatomical variability exists, like the median nerve at the elbow or the sural nerve (Choi et al., 2019; Kamm et al., 2009; Pyun and Kwon, 2008; Savastano and Yang, 2015), the USG improved amplitude recorded

or SMI delivered. Other studies have found an improvement of amplitude or intensity with the USG for the non-routine nerves recorded or nerves with anatomical variability (Kamm et al., 2009; Park et al., 2015). In our study where US guidance was provided, practitioners appeared to be more likely to perform non-routine muscle punctures using US (n = 64, 44 %) than with sham US (n = 43). The most commonly chosen muscles were the psoas and teres pronator muscles (40 versus 1 and 21 versus 13, respectively), the other muscles were too infrequently punctured to identify a difference between the two groups. USG muscle has been used to facilitate muscle biopsies increase the accuracy of standard needle electromyography (EMG) for non-routine muscles such as the extensor indicis muscle and tibialis posterior, for plegic muscles, for junior resident physicians or scanning EMG (Billakota et al., 2016; Connell et al., 2023; Elleuch et al., 2021a, 2021b; Gentile et al., 2020; Karvelas et al., 2016; Maitland et al., 2022; Padua et al., 2023). In the study on residents, needle electrode placement accuracy improved with residency years. Accuracy increased for the soleus and peroneus longus, from 60 % to 100 %, and for the teres pronator muscle from 60 % to 85.7 % (Karvelas et al., 2016). In cadaver studies, USG improved accuracy from 71.9 % to 96.7 % and 39 % to 96 % (Boon et al., 2011b; Yun et al., 2015).The improvement was greater for muscles that are rarely targeted, deep, or at high risk (close to vascular structures) or in cases with altered anatomical landmarks (Boon et al., 2011b). In our study, practitioners more often chose to puncture the teres pronator muscle or psoas which are located close to potentially damaging vascular structures, when they were able to use USG safely. The use of USG can make practitioners more confident in their electroneuromyographic explorations.

Strengths and limitations.

The examination time was only 5 min longer in the USG group. USG thus seems easily feasible during NCS. Although the inexperienced US practitioners underwent a short training time, they could identify all the nerves. This reinforces the feasibility and generalization of the USG practice in NCS. No difference in pain sensation was found in the two groups, as in Cartwright et al. (Cartwright et al., 2019). The patient described the exam as painless or painless in 95.2 % of cases, which is reassuring for an exam that is often considered to be painful (Gans and Kraft, 1977; Strommen and Daube, 2001; Wee et al., 2004).

In our study, all neurophysiological practitioners had more than three years' experience. Expertise in standard NCS and anatomical knowledge could limit the variability of the stimulation site in healthy subjects. A learning curve is possible. We gradually revised the stimulus site for all NCS of the median nerve at the elbow after noticing that the US often found it more lateral than expected. The US training time was relatively short. A longer time could improve performance, at least on the sural nerve, which had a higher SNAP in the US expert subgroup. Altogether, these factors likely minimized the differences between the two groups. We randomized our patients, although previous studies used the patient as their own control (Cartwright et al., 2019; Choi et al., 2019; Kim et al., 2017; Wei et al., 2021), limiting the comparability to the published literature. We can determine an improvement in amplitude or SMI between groups, but not at the level of the individual. This choice may have masked a possible effect due to the high inter-individual variability.

5. Conclusion

These results do not justify performing systematic USG in all healthy participants, when performed by experienced practitioners. Even if significant differences on intensity are found on certain nerve with US, these differences are too low to be appreciated by the patient. The USG did not improve patient's tolerance of NCS. However, the USG is beneficial for some nerves with more anatomical variability or in obese patients to limit the stimulation intensity and to identify the optimum stimulation site. For the sural SNAP in normal NCS, the amplitude's difference with US could impact the NCS results. We propose the use of USG when the responses with standard NCS are lower than the clinical history and examination suggested. The US extends the duration by only a few minutes and can therefore be easily integrated into an NCS. The USG could be a greater help to eliminated a technical deficiency related anatomical variability or obesity. The USG provides reassurance to practitioners who are more willing to puncture non-routine muscles. Novice NCS practitioners, with poorer anatomical knowledge, could benefit more from USG. Further studies ought to be carried out to test the best application of this technique.

CRediT Author Contribution Statement

Marie Laure Inghilleri: Investigation; **Sandrine Alonso:** Methodology; **Hélène Moron:** Investigation; **Hector Ruiz:** Investigation; **Sophie Bastide:** Methodology, Conceptualization; **Sarah Coudray:** Conceptualization, Writing, supervision.

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Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with the guidelines

Conflict of interest

None of the authors has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cnp.2024.01.003.

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