Original Article

Muscle ultrasound in assessment of critical illness neuromyopathy in comparison with nerve conduction

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ABSTRACT

Purpose: To evaluate the diagnostic role of muscle ultrasound compared to nerve conduction studies in critical illness neuromyopathy (CINM). Subjects and Methods: 20 patients with SOFA score > 3 points were included in a prospective, randomized study done in the critical care department and subjected to muscle ultrasound on day 7 and 14 and nerve conduction studies (NCS) on day 14, also 20 healthy controls were examined by muscle ultrasound on days 7 and 14. Results: Muscle echogenicity and fasciculation were significantly higher on day 14 than day 7. They were negatively correlated with NCS. By ROC curve, the muscle echogenicity on day 14 was the best diagnostic tool for neuromyopathy in critical ill patients. The sensitivity & specificity of muscle echogenicity and fasciculation on day 14 were 94.1% and 100% as well as 88.4% and 100%, respectively. On day 7, the sensitivity and specificity of muscle echogenicity were 94.1% and 66.7%, respectively. Conclusion: The muscle echogenicity and fasciculation were non-invasive good tools in the evaluation of neuromyopathy in critical ill patients in comparison with NCS.

Keywords: Muscle ultrasound, Nerve conduction studies, critical illness neuromyopathy

Introduction

Patients in the Intensive Care Unit (ICU) are at risk for developing ICU acquired weakness [1], with prevalence of up to 65%. During the first week of critical illness, muscle wasting occurs and is more severe in multi-organ than single organ failure patients [2]. Typically, patients develop generalized muscle weakness with lost deep tendon reflex and distal sensory reduction, and even respiratory muscle are affected [3-5].

The current standard of diagnosis consists of muscle strength assessment using the Medical Research Council (MRC) scale together with nerve conduction studies (NCS) and electromyography (EMG) [6]. The electrophysiological studies (EDX) showed reductions of the amplitude of compound muscle action potentials and sensory nerve action potentials in CIP [6]. While in CIM, there is normal sensory nerve action potentials [6]. However, EDX are difficult to conduct in ICU due to the presence of edema, inadequate voluntary muscle contraction, and electrical interference [7].

Also, muscle strength assessment (MRC) is frequently delayed because of impaired consciousness, due to sedation. These data limited the clinical applicability of MRC in critically ill patients [8]. Thus, the need of noninvasive and applicable muscle assessment is pressing to allow early diagnosis and intervention that can improve outcome [9]. Muscle ultrasound allows bedside muscle assessment [10]. It is painless, non-invasive, inexpensive and readily accessible in ICU. It adds information about structural changes and spontaneous activity of muscles [11]. The changes in muscle echotexture in those with acute conditions can occur early and may be detected easily by ultrasound [10].

Aim of the work

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This study evaluates diagnostic role of muscle ultrasound - compared to nerve conduction studies- in critical illness neuromyopathy (CINM).

Patients and Methods

This prospective study included twenty critical ill patients who were admitted to Critical Care Unit of Kasr AL-Ainy Hospital, Cairo University with multi-organ failure (SOFA score > 3 points) during the period from July 2015 to March 2017 and twenty healthy controls who were either from the healthy individuals accompanying the patients during their visits to the hospital or from the hospital staff. They were subjected to full neurological and medical examination to verify their normality. Muscle ultrasound was done for all these controls.

The study excluded patients with history of high-dose steroid therapy or neuromuscular blockers, stroke, CNS infection or neuromuscular disorder for example (myopathy and motor neuron disease), diabetic neuropathy, terminal malignancy and finally patients with traumatic brain or spinal injury.

All included patients were subjected to proper history taking and full clinical examination. Laboratory investigations performed included CBC (complete blood count count), coagulation profile, ABGs (arterial blood gases), liver function tests (LFTs) and kidney function tests.

Scoring system utilized included: Sequential organ failure assessment (SOFA) on admission in days 7 and 14. The score is based on six different scores (respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems). Each one ranges from zero to 4 points**,** so total score ranges from zero to 24 points [12].

Nerve conduction studies were done on day 14 using a portable electrophysiologic device deymed (trutrace) in czech republic & Germany with surface electrodes. The ulnar nerve and tibial nerve were measured. Motor and sensory nerve responses were assessed for the ulnar nerve and motor responses for the tibial nerves [13]. Myogenic insult was favored with affection of the motor nerve conduction studies yet normal sensory nerve conduction studies. Neuropathic affection was favored with both fibres were affected.

The measurement of ulnar nerve CMAP amplitude was recorded using a pair of surface electrodes that was placed over the muscle belly and the fifth metacarpal phalangeal joint. The ulnar nerve was stimulated over medial wrist adjacent to the flexor carpi ulnaris tendon, below elbow at 3-4 cm distal to the medial epicondyle, above elbow over the medial humerus and medial to the biceps over the axillary phase.

The tibial nerve CMAP amplitude was recorded using a pair of surface electrodes that was placed over abductor hallucis brevis muscle. The tibial nerve was stimulated above and posterior to the medial malleous and midposterior knee over the popliteal pulse. The stimulus intensity of both ulnar and tibial nerves was gradually increased until the maximal CMAP was obtained. The CMAP amplitude was measured as the maximum voltage difference between the negative and positive peaks

Ultrasound was used to obtain muscle images on days 7 and 14 using a 9 to 13 MHz probe real-time linear array scanner (Siemens). The device settings included gain of 90 & width of 40 mm, and were kept constant during all examinations, while the depth was altered individually for rare occasion when development of large amount of subcutaneous edema require slightly deeper view to visualize entire muscle. Patients were examined in the supine position with extended upper, lower limbs and relaxed muscles. Compression of the tissue was avoided as it can affect the quality of muscle images. Different muscles were examined in both axial and longitudinal planes; Bicebs brachii and quadriceps femoris muscles at the midline between origin and insertion, the extensor muscles of the forearms at the first third of the distance between the elbow and processus styloideus radii and the tibialis anterior muscle at one the fourth distance from the inferior edge of patella to the lateral malleolus. Transverse images of each muscle were obtained with the transducer perpendicular to the direction of muscle fiber orientation, and longitudinal images of each muscle were obtained with the transducer parallel to the muscle fiber direction.

The muscle echogenicity was assessed by muscle ultrasound and graded according to Heckmatt and colleagues [14] into four grades:

(**Grade 1**) Normal echo intensity with starry-night aspect with distinct bone echo.

(**Grade II**) Increased echo intensity with normal bone echo.

(**Grade III**) Increased echo intensity with reduced bone signal.

(**Grade IV**) Increased echo intensity and loss of bone signal **(Figure 1)**.

The muscle fasciculations were detected by ultrasound. Each muscle was examined over a time period of 10 seconds. The movement of fasciculation was defined as twitching of small parts of the muscle lasting for 0.2–0.5 s, at least two of which were required to be classified as being present and it can be differentiated from arterial pulsations (unifocal, rhythmic) or voluntary movements (involving the entire muscle) [15]**.** A fasciculation score that ranged from 0 to 4 that is number of regions with fasciculations out of four muscle regions. Complete ultrasonographic examination of each patient was performed in 20 minutes.

Ethical committee approval: It was ethically approved by the Critical Care department- Faculty of Medicine -Cairo University.

Statistical methods:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparison of serial measurements within each patient the

non-parametric Wilcoxon signed rank test was used. For comparing categorical data, Chi-square (c2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlations between quantitative variables were done using Spearman correlation coefficient. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of different variables for detection of bad outcome. P-values less than 0.05 were considered as statistically significant [16].

Results

A total of twenty patients were eligible for enrollment in this study; 60% were female, with age ranged from 32 to 75 years (mean = 56.57). Six patients (30%) had diabetes mellitus. They were admitted to the ICU having the following diagnoses: sepsis (30%), septic shock (40%), hypovolemic shock (15%) and ARDS (15%). They were diagnosed according to nerve conduction studies to have CIP (60%), CIM (25%), and normal NCS (15%) (**Table 1)**.

Echogenicity of examined muscles and Fasciculation score were significantly higher on day 14 than day 7 **(Table 2).**

Comparison between muscle ultrasound data of patients and controls

20 healthy controls (mean age 51 years, with a range from 35 years to 70 years; 12 males, 8 female) were examined.

The mean echogenicity of biceps brachii, quadriceps femoris and tibialis anterior muscles were higher in patients on day 7 compared to control, with statistically significant difference (p-value 0.06, < 0.001 &0.002). Also there were high statistically significant differences in the mean echogenicity of all examined muscles of patients on day 14 & controls (p-value < 0.001).

The mean fasciculation score was higher in patients on day 14 than controls with statistically significant difference (p-value 0.001), while there was no significant difference in the mean fasciculations between patients on day 7 & controls (p value 0.383) (**Table 3).**

Correlation between muscle ultrasound and NCS

Mean muscle echogenicity on day 7 showed significant negative correlation with ulnar CMAP and NCV (p 0.035, r -0.474 and p 0.047, r -0.474, respectively) and strong negative correlation with tibial CMAP and NCV (p 0.002, r-0.641 and p 0.003, r-0.670, respectively). On day 14, it showed stronger negative correlation with ulnar CMAP (p 0.015, r -0.537), with tibial CMAP and NCV (p<0.001, r-0.726 and p 0.001, r -0.745, respectively) (**Table 4).**

The mean muscle fasciculations on day 7 was negatively correlated only with ulnar NCV (p 0.041, r-0.485). On day 14, The mean muscle fasciculations was negatively correlated with ulnar CMAP (p 0.011, r -0. 553), tibial CAMP (p 0.003, r -0.625) and tibial NCV (p 0.011, r -0.598) **Table (5).**

Predictive data (sensitivity and specificity)

Validity of muscle ultrasound data (echogenicity and fasciculation) as diagnostic tools of patients with of critical illness neuromyopathy.

The muscle echogenicity on day 14 was the best diagnostic tool for neuromyopathy in critical ill patients at cutoff point of 1.5 where AUC was 0.971, p 0.011, sensitivity 94.1% and Specificity 100%. Also, the muscle echogenicity on day 7 was a good diagnostic tool for at cutoff point of 1.4 where AUC was 0.892, p 0.034, sensitivity 94.1% and Specificity 66.7%. The muscle fasciculation on day 14 was the same as the muscle echogenicity where cutoff was 0.5, AUC 0.941, sensitivity 88.4% and Specificity 100% (**Table 6 and Figure 2).**

Discussion

Muscle ultrasound data showed that, the mean echogenicity of examined muscles increased on day 14 as compared to day 7 with statistically significant difference. Our results agree with the work done by **Grimm et al.** [11]**.** They studied patients with sepsis and found that the mean echogenicity in patients increased between days 4 and 14.

In our study, muscle fasciculations were detected on day 7 but were more prominent on day 14 as fasciculations increased over time of critical illness. Our result is consistent with finding of **Grimm et al**. [11] who found that patients with sepsis on day 14 had more fasciculations than patients on day 4. Also, in study by **Hund et al.** [17]**,** it has been shown that the median time to develop grade 2 to 3 fasciculations was 21 days after ICU admission, with earliest occurrence of grade 1 fasciculations on day 8 and grade 2 fasciculations on day 11. In patients admitted with sepsis grade 3 fasciculations were already present at the initial examination on day 4 [17]**.**

In our study, it is worth mentioning that the ultrasound findings showed significant correlations with NCS results. Muscle echogenicity changes in critical ill patients correlated early on day 7 with the NCS abnormalities (ulnar CMAP, ulnarNCV, tibial CAMP and tibial NCV) while muscle fasciculations correlated later on day 14. These correlations may be attributed to increased muscle echogenicity that was denoting replacement of normal tissue with fibrous or adipose tissue. This signifies decreasing of tissue excitability, so CMAP was reduced. The muscle fasciculations were detected because of denervation hypersensitivity that also means a decrease in tissue excitability. Thus, according to our results it is postulated that there was correlation between muscle morphology (that was detected by muscle ultrasound) and the physiology.

In study by-Christopher et al, it was found that amplitude of CMAPs was abnormal in 100% of 44 patients with intensive care unit acquired weakness (ICU-AW). All patients showed markedly increased CAMP duration, and these parameters have an high specificity and sensitivity for diagnosis of myopathic involvement in critical illness neuromyopathy [18]**.** According to these results, the correlations between CMAP, muscle echogenicity and fasciculations support role of muscle

ultrasound in diagnosis of critical illness neuromyopathy (CINM).

In our study, the muscle echogenicity (days 7 & 14) and fasciculations (day 14) were good diagnostic tools for critical illness neuromyopathy. Other studies evaluated the accuracy of qualitative muscle ultrasound in the discrimination of normal muscle from myopathic, neurogenic, and unspecifically abnormal tissue changes in the suspected neuromuscular disease (NMD) in childhood. **Zuberi et al.** [19] examined muscle echogenicity, using Heckmatt's criteria. The sensitivity of ultrasound in detecting neuromuscular disease was 81% with 96% specificity. In other study by **Brockmann et al.** [20] who found a sensitivity of 81% and a specificity of 96% for detection of any abnormal muscle tissue alteration by ultrasound. Also **Rahmani et al.** [21] reported that ultrasound can differentiate between children with neuromuscular and those with non-neuromuscular diseases with a sensitivity of 92%, and specificity of 90%

Limitations

The current study has some limitations. First, muscle ultrasound was done on days 7 & 14. Additional evaluation of muscle ultrasound from day 0 till discharge may be needed for more description of ultrasonic muscle changes. second, ultrasound data included only muscle echogenicity and fasciculations. Additional parameters such muscle thickness (diameter, area, and volumes of the muscles) were not described. Third, echotexture grading using the Heckmatt score may be subject to technical misinterpretation in contrast to the gray-scale histogram. However, this score used in our study is a rapidly applicable that can be easily done by intensivist physician. Finally, muscle biopsy was not done as it is invasive with potential for complications

Table 1. Demographics and baseline characteristics of patients

Age(years)	56.57
Female gender	60%
Diabetes	30%
Sepsis	30%
Septic shock	40%
Hypovolemic shock	15%
ARDS	15%
CIP	60%
CIM	25%
Normal NCS	15%
APACHE score	17.50± 8.59
SOFA score d7	8.10± 2.69
SOFA score d14	9.00±6.53
Days of ICU stay	19.95± 5.19
Duration of ventilation	9.05±7.98
Mean of net fluid balance d7	-1818 ml
Mean of net fluid balance d14	-2230 ml

ARDS: Adult respiratory distress syndrome, CIP: Critical illness polyneuromyopathy

CIM: Critical illness polyneuromyopathy, NCS: Nerve conduction study

Table 2. Mean values of muscle ultrasound data

	Day 7		Day 14		P value
	Mean	SD	Mean	SD	
Echogenicityof biceps	1.65	0.59	2.30	0.80	**0.003**
Echogenicity of extensors	1.40	0.50	2.10	0.85	**< 0.001**
Echogenicity ofquadriceps	2.05	0.60	2.85	0.88	**< 0.001**
Echogenicity of tibialis	1.60	0.50	2.35	0.93	**0.002**
fasciculation score	0.50	0.61	1.75	1.37	**0.001**

Table 3. Comparison between muscle ultrasound data of patients and controls

	Patients		Controls		
	Mean	SD	Mean	SD	P value
Echogenicityof biceps d7	1.65	0.59	1.05	0.22	**0.002**
Echogenicity of biceps d14	2.30	0.80	1.05	0.22	**< 0.001**
Echogenicity of extensors d7	1.40	0.50	1.05	0.22	0.06
Echogenicityof extenors on d14	2.10	0.85	1.05	0.22	**< 0.001**
Echogenicity of quadriceps d7	2.05	0.60	1.20	0.41	**< 0.001**
Echogenicityof quadriceps d14	2.85	0.88	1.20	0.41	**< 0.001**
Echogenicity of tibialis d7	1.60	0.50	1.05	0.22	**0.002**
Echogenicityof tibialis d14	2.35	0.93	1.05	0.22	**< 0.001**
Fasciculations d7	0.50	0.61	0.30	0.47	**0.383**
Fasciculations d14	1.75	1.37	0.30	0.47	**0.001**

Table 4. Correlation between muscle echogenicity and NCS

		Echogenicity d 7	Echogenicity d 14
Ulnar CMAP	**R**	-0.474	-0.537
	P	.0035	0.015
Tibial CMAP	**R**	-0.641	-0.726
	P	0.002	<0.001
Ulnar NCV	**R**	-0.474	-0.334
	P	0 .047	0 .176
Tibial NCV	**R**	-0.670	-0.745
	P	0 .003	< 0.001

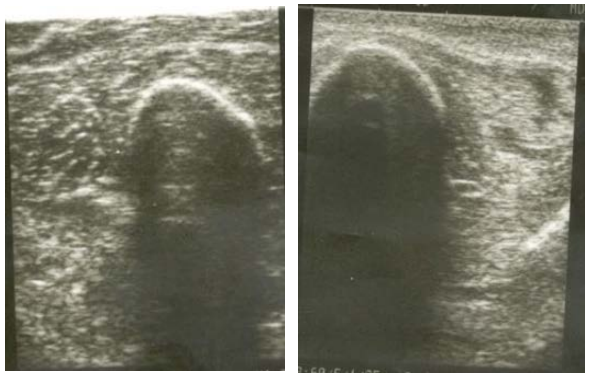
CMAP: compound motor action potential, NCV: nerve conduction velocity

Table 5. Correlation between muscle fasciculations and NCS

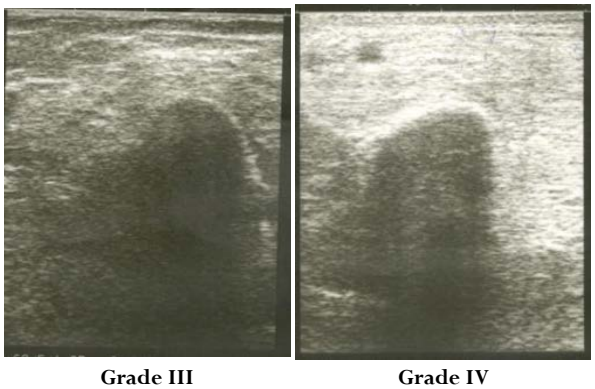
		Fasciculation d 7	Fasciculation d14
Ulnar CMAP	R	-0.313-	-0.553-
	P	0.179	0.011
Tibial CMAP	R	-0.146-	-0.412-
	P	0.540	0.071
Tibial CMAP	R	-0.292-	-0.625-
	P	0.211	0.003
Ulnar NCV	R	-0.485-	-0.259-
	P	0.041	0.299
Tibial NCV	R	-0.258-	-0.598-
	P	0.317	0.011

Table 6. Muscle echogenicity and fasciculation as diagnostic tools of patients with of critical illness neuromyopathy

Test Result Variable(s)	Area under curve	P value	95% Confidence Interval		Cutoff value	Sensitivity (%)	Specificity (%)
			Lower Bound	Upper Bound			
Echogenicity d 7	0.892	0.034	0.695	1.090	1.375	94.1	66.7
Echogenicity d 14	0.971	0.011	0.898	1.044	1.5	94.1	100
Fasciculation d 7	0.765	0.153	0.539	0.991	----	-----	----
Fasciculation d 14	0.941	0.017	0.837	1.046	0.5	88.4	100



Grade I Grade II



Grade III Grade IV

Figure 1. Ultrasound of biceps brachii muscle showing different grades in echogenicity as defined by the Heckmatt score

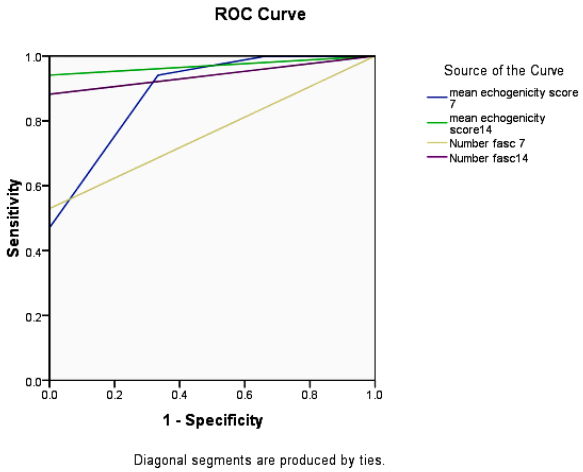


Figure 2. The Roc curve of muscle echogenicity and fasciculations(fasc) in diagnosis of critical illness neuromyopathy

Conclusion and Recommendations

The muscle echogenicity (day 7 and14) and fasciculations (day 14) were a non invasive good tools inthe evaluation of neuromyopathy in critical ill patients in comparison with NCS. We recommend that muscle ultrasound can be used for screening of critical ill patients for early detection of myopathy.

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Abbreviation key

ARDS**:** Adult respiratory distress syndrome
CIM: Critical illness myopathy
CIMN: Critical illness neuromyopathy
CIP: Critical illness polyneuropathy
CMAP: Compound motor action potential
EDX: Electrophysiological studies
EMG: Electromyography
ICU: Intensive care unit
MRC: Medical research council
NCS: Nerve conduction study
NCV: Nerve conduction velocity
NMD: Neuromuscular disease
SOFA: Sequential Organ Failure Assessment.

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