THE EFFECTS OF ANODAL IONTOPHORESIS OF EPINEPHRINE ON NEUROMUSCULAR RESPONSES IN HEALTHY MEN AND PATIENTS WITH MYASTHENIA GRAVIS

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Abstract- Iontophoresis of epinephrine for assessment of neuromuscular junction response is a new technique that can improve diagnose of neuromuscular dysfunction. The purpose of this study was to investigate the effects of iontophoresis of epinephrine on neuromuscular junction response. Iontophoresis of epinephrine solution (1mg/ml), sodium chloride, calcium gluconate, epinephrine with sodium chloride and distilled water was applied in five groups of healthy men and 7 patients with myasthenia gravis (MG). Amplitude, depolarization, repolarization and recovery times and slops of compound muscle action potential (CMAP) were measured. Also low repetition stimulus tests were applied before and after iontophoresis of epinephrine. Following results were obtained: 1) iontophoresis of sodium ion increased depolarization time, and iontophoresis of sodium and calcium ions increased recovery and duration times of CMAP, 2) slope of depolarization and recovery were reduced by iontophoresis of active ions, 3) iontophoresis of epinephrine increased slope of recovery or Na-K transport at 10 and 15 minutes after iontophoresis, 4) iontophoresis of epinephrine in patients with MG reduced amplitudes of all CMAPs and percentage of decrement between first and fifth signal increased at low frequency stimulus test, and 5) iontophoresis of epinephrine in normal group increased percentage of amplitude increment between first and fifth signal in low frequency stimulation test. Neuromuscular responses in patients with MG in comparison to normal men are sensitive to iontophoresis of epinephrine and demonstrate significant decrement findings to low repetition stimulus tests. Iontophoresis of epinephrine with RNS tests can be useful in assessments of these patients.

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Key words: Myasthenia gravis, iontophoresis, epinephrine, neuromuscular junction

INTRODUCTION

All the muscle fibers supplied by one motor nerve, together with the neuron from which the nerve originates, constitute a motor unit. The number of muscle fibers innervated by a single nerve fiber determines the flexibility of the response that it is capable.

Each muscle fiber obeys the 'all-or-none' law. Therefore, each fiber will either contract in response to a stimulus or fail to do so (gradation of muscle contraction is due to the less sensitive muscle fibers within a single muscle failing to respond). Under the usual physiological conditions, all the muscle fibers in a motor unit contract together and have a similar threshold of excitability (1). Multiple nonpharmaceutic methods exist for neuromuscular junction tests. The most common and widely used method is low and

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high frequency stimulus test. Patients with neuromuscular junction disease are not sensitive to this test at the onset of illness or after long term treatments, and intravenous injection of neuromuscular blocking agents with or without local ischemia are necessary (2).

Iontophoresis of drugs is a method for delivery of pharmacologic agents. Avoidance of adverse effects on the gastrointestinal system when these same agents are introduced into the body orally is one example (3). Following oral or parenteral administration and alimentary absorption of drugs, they are transported through the portal system to the liver where they may be metabolized. Alternative methods such as iontophoresis, phonophoresis or passive permeation minimize the metabolism of drugs by the liver, thus avoiding this first-pass effect (4). Transcutaneous pharmacologic delivery also provides the potential for localized delivery to the tissue underlying the site of application. Iontophoresis has been documented to transcutaneously deliver a variety of pharmacologic agents under either experimental or clinical conditions. Transcutaneous deliveries of polar and nonpolar agents of either small or large molecular weight have been documented (1).

A recent experiment documented that iontophoresis of ketoprofen (NSAID) enhances permeation into the fascia-muscle interface (4). Armstrong and Lester used iontophoresis of tubocurarine in rana pipiens sartorius and cutaneous pectoris muscles. They showed that tubocurarine inhibits the release of acetyl choline and decreases the neuromuscular junction responses (5). Min and Bekavac applied iontophoresis of gallamine, rocuronium, d-tubocurarine, atracurium, vecuronium, pancuronium and doxacurium on frog neuromuscular junction. They demonstrated that when muscle relaxants were applied directly by iontophoresis on the end plate, the speed of both onset and offset of action was depended on the drug that was applied (6). Clausen and Flatman reported effects of catecholamines on Na^+-K^+ transport and membrane potential in rat soleus muscle. Their experiments indicated that adrenaline increased Na efflux and K influx. Similar effects were exerted by noradrenaline, phenylephrine, salbutamol and isoprenaline. Also it was concluded the active electrogenic Na-K transport is susceptible to stimulation by catecholamines via β-adrenoceptors (7, 8). Drummond and Lipnicki explained effect of noradrenaline and saline by iontophoresis in 19 healthy subjects. They concluded that repeated iontophoresis of noradrenaline or saline inhibited vasoconstriction to noradrenaline (9). Neurochemical, neuroautonomic and neuropharmacological assessments carried out on all myasthenia gravis (MG) patients showed that they present a neural sympathetic deficit plus excessive adrenal-sympathetic activity. These abnormalities were registered during the basal (supine-resting) state, as well as after several stress tests (orthostasis, exercise, oral glucose and buspirone). In addition, MG patients showed increased levels of free-serotonin (f-5HT) in the plasma, supposedly associated with the increased platelet aggregability which was found in all MG patients. As the above trio of neurochemical disorders (low noradrenergic-activity, high adrenergic-activity and increased f-5HT plasma levels) is known to favor Th-1 immunosuppression and Th-2 predominance, Lechin and coworkers outlined a neuropharmacological strategy for reverting the above neurochemical disorder. This treatment provoked sudden (acute) and late sustained improvements. Acute effects have been attributed to the increase of alpha-1 activity at the spinal motoneuron level. Late improvements always parallel a significant normalization of immunological disorders. Complete normalization was registered only in non-thymectomized MG patients (10).

Repetitive nerve stimulation (RNS) is a simple and rapid method for evaluation of neuromuscular transmission defects. Although the effect of exercise in conjunction with RNS is well recognized, it has not been standardized in actual patient and control groups. The standardized use of exercise with RNS is advocated for increasing its diagnostic yield in the neurophysiologic laboratory (11).

Iontophoresis of epinephrine for assessment of neuromuscular junction response is a new technique that can improve for other drugs in relation to interpretation or diagnose of neuromuscular dysfunction. The aim of this study is to determine

the effect of iontophoretic application of epinephrine on neuromuscular junction, especially postsynaptic responses in normal men and patients with MG.

MATERIALS AND METHODS

Apparatus

Toennies EMG (model NeuroScreen) was used. The neuromuscular response was recorded with band pass filtered between 5 Hz and 5 kHz. Enraf Dynatron 438 was used for iontophoresis. Laser Doppler flowmeter model MBF3D (Moor Instrument) with surface connection probe number 7 was used for measuring blood flux.

Drugs

One mg/ml Epinephrine solution (Darou Pakhsh co.), 10% sodium chloride (Razi co.), 0.9% calcium gluconate (Pars co.) and distilled water (Sobhan co.) for iontophoresis and direct current were obtained. These drugs and ions solutions were added to a hydrophilic pad that was soaked by water without salts.

Methods of recording

Fifty three healthy male volunteers with no history of neuromuscular disease after being informed about conditions of tests and 7 patients (3 women and 4 men) with MG referred by neurologist participated in the following groups:

1- Normal subjects

I- Iontophoresis of epinephrine solution.

II- Iontophoresis of sodium chloride.

III- Iontophoresis of epinephrine and sodium chloride.

IV- Iontophoresis of gluconate calcium.

V- Direct current or iontophoresis without ions (distilled water).

VI- Iontophoresis of epinephrine solution before low RNS.

2- Patients subjects

I - Iontophoresis of epinephrine solution before low RNS.

The abductor hallucis of dominant foot was tested in supine position with neutral position of ankle joint. Skin temperature with digital thermometer was recorded during tests by placing transducer on the medial region of dominant foot. Surface recording electrodes were placed on the abductor hallucis muscle. A standard bipolar electrode (1-cm diameter with 3-cm separation between cathode and anode) was placed on muscle belly and secured with tape. Site of electrode was marked and measured, so that electrode placement could be duplicated in second testing session. A ground electrode was placed on medial malleolus. Surface stimulus electrode was placed behind and proximal to medial malleolus at 8 cm from active recording electrode. Tibial nerve was stimulated supra maximally with 0.5 msec pulse duration at a selective interval before iontophoresis.

Muscle action potential of abductor hallucis was recorded before iontophoresis and after it, at one (T1), five (T5), ten (T10) and fifteen (T15) minutes in five stages and percentage changes of amplitude of compound muscle action potential (CMAP) were also recorded following RNS test in sixth stage.

Amplitude (negative and positive), distal latency, duration, times and slopes of depolarization, repolarization, recovery or Na/K transport before and after of iontophoresis were measured in five groups (Fig. 1, 2). Decrement or increment amplitude of fifth to first CMAP was measured by software of EMG apparatus following RNS test for both normal and patient groups.

Skin blood supply of eight subjects at side of iontophoresis of epinephrine was recorded by laser Doppler, at five minutes before and fifteen minutes after delivery of epinephrine.

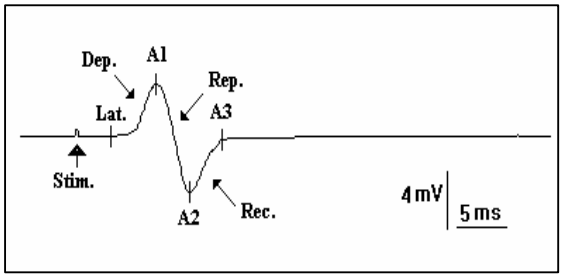

Fig. 1. Amplitudes of negative (A1) and positive (A2) peaks, depolarization (Dep), repolarization (Rep), recovery (Rec) times and slopes duration (A3-Lat) of one CMAP of Abd. Hallucis muscle.

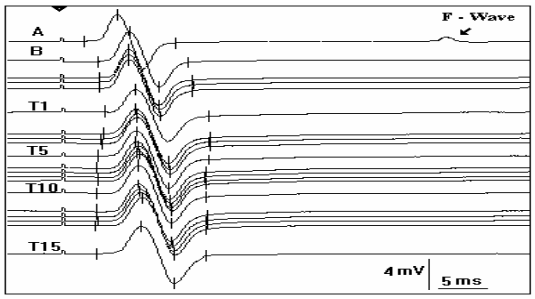

Fig. 2. Recording of CMAPs of abductor hallucis before and after iontophoresis of epinephrine and other ions. Supra maximal stimulation with F wave response for detection of nerve stimulus intensity (A). Parameters of CMAP before iontophoresis with same intensity (B), and after iontophoresis at one (T1), five (T5), ten (T10), fifteen (T15) minutes later.

Iontophoresis technique

All of above groups accepted 50 mA.min. direct current for delivery of epinephrine and other ionic solutions on abductor hallucis brevis muscle of right foot.

Active electrode for drug transfer was positive (1.5 - 4.5 cm) and placed on a hydrophilic pad (2 - 5 cm) that was saturated by epinephrine solution or other ionic solutions. After recording initial CMAPs and neuromuscular junction responses, this active electrode was placed on a hydrophilic pad on the abductor hallucis muscle area. Negative or inactive electrode (5-10 cm) was attached completely on medial region of leg at the same lower extremity at 25 cm proximal to positive electrode.

RESULTS

Parameters of CMAP and RNS tests before and after iontophoresis of epinephrine or other ionic solutions and direct current (distilled water) were compared with Friedmann and Wilcoxon tests. Mann-Whitney and Kruskal Wallis 1-way ANOVA were used for independent nonparametric tests.

Iontophoresis of active ions

1- Amplitudes of CMAPs did not show changes with iontophoresis.

2- Distal latencies of CMAPs were not significantly changed by iontophoresis.

3- Depolarization times of CMAPs were significantly increased after application of iontophoresis ($P < 0.05$) (Table 1).

4- Depolarization slope of CMAPs was significantly decreased after application of iontophoresis of sodium chloride ($P < 0.05$) but it showed no change in iontophoresis of epinephrine group (Fig. 4, Table 2).

5-Repolarization time in iontophoresis of sodium chloride was increased and indicated significant changes ($P < 0.05$)

6-Repolarization slope after iontophoresis of sodium chloride was changed ($P < 0.05$).

7-Iontophoresis of active ions increased markedly recovery time at all times after end of iontophoresis ($P < 0.05$) (Fig. 5), but iontophoresis of epinephrine didn't change this time ($P < 0.05$).

8- Slopes of recovery stage or Na-K transport following iontophoresis of active ions were reduced significantly ($P < 0.05$), but iontophoresis of epinephrine increased slope of Na-K transport at 15 minute after iontophoresis ($P < 0.05$) (Fig.6, Table 2).

9- Duration of CMAPs was increased significantly following iontophoresis ($P < 0.05$).

10- There were not significant changes in parameters of CMAPs following direct current with distilled water, except slope of repolarization which indicated significant difference at T1 time.

11- Significant difference between epinephrine and other ions in changes of slope and time of recovery stage or Na-K active transport were seen.

12– In normal subjects, (RNS test) iontophoresis of epinephrine did not show significant effects on peak to peak amplitudes of first CMAP, but amplitudes of fifth CMAP increased immediately after end of iontophoresis and comparison to pre test indicated significant difference ($P < 0.05$).

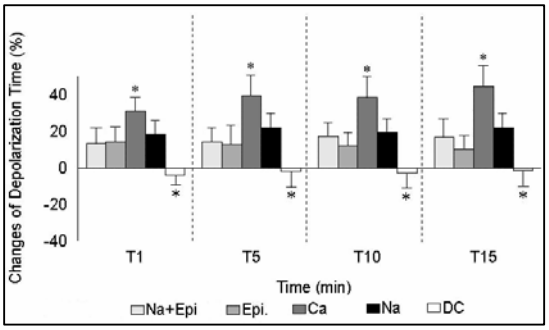

Fig 3. Mean ± SEM of changes of depolarization time after iontophoresis of different ions. Increase of depolarization appeared after iontophoresis. Comparison between epinephrine effect and Ca ion and distilled water indicated significant different (* = $P < 0.05$).

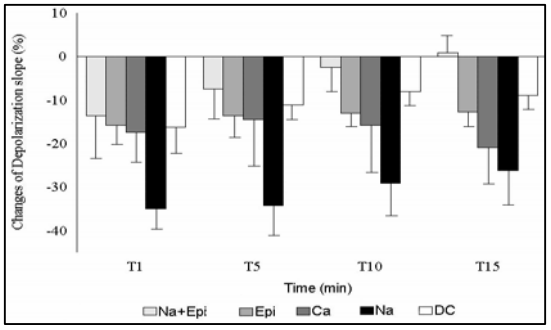

Fig 4. Mean ± SEM of changes of depolarization slope after iontophoresis of different ions. Reduce of depolarization slope appeared after iontophoresis in all conditions and there are not any significant difference between them.

13- In RNS test amplitudes of fifth CMAP after iontophoresis in comparison to first CMAP in normal subjects, at all the times showed significant increase ($P < 0.05$) (Fig. 7-8).

14- In patients, comparison of peak to peak amplitudes indicated significant difference between pre and post iontophoresis immediately after end of iontophoresis (T1) in both first and fifth CMAP ($P < 0.05$), and amplitudes of fifth CMAP in comparison to first at T1, T5, T10 and T15 times were depressed but at pre test increase of amplitude of fifth CMAP appeared ($P < 0.05$). Amplitudes of first and fifth CMAPs in patients depressed markedly after iontophoresis of epinephrine. In normal subjects comparison of amplitude difference between fifth and first CMAP indicated that percentage of differences following low repetition stimulus test has increased (Fig. 7).

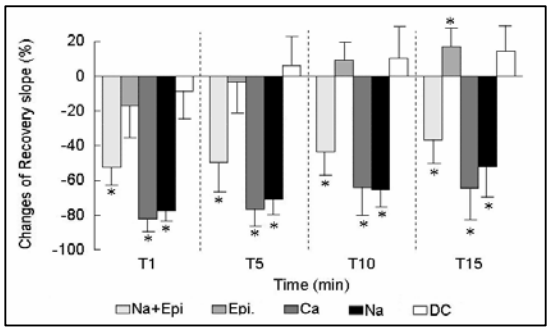

Fig 6. Mean ± SEM of changes of recovery slope or speed of Na-K transport activity after iontophoresis of different ions. Reduction of recovery slope appeared after iontophoresis. Comparison between epinephrine effect and Ca and Na ions and combination of Na with epinephrine indicated significant different. Epinephrine at T15 increased speed of Na/K transport with significant different (*= $P < 0.05$).

Iontophoresis of epinephrine elevated this increment immediately after end of iontophoresis due to increase of amplitude of fifth CMAP, and this increase maintained up to ten minutes after iontophoresis. In patients, iontophoresis of epinephrine reduced amplitude of fifth signal and decremental findings were seen in low repetition stimulus test at immediately after end of iontophoresis, whereas before iontophoresis of epinephrine these patients had normal incremental findings at this test (Fig. 9, 10).

15- Decremental findings in patients maintained up to fifteen minute and showed significant difference in comparison to before iontophoresis of epinephrine ($P < 0.05$).

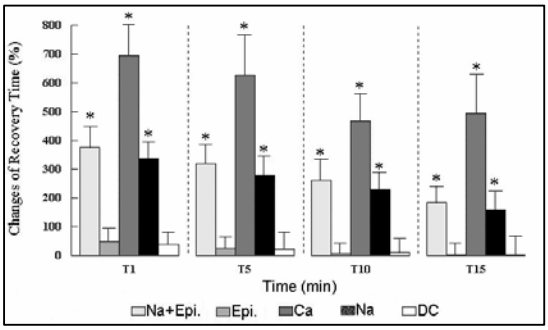

Fig 5. Mean ± SEM of changes of recovery time or Na/K transport after iontophoresis of different ions. Increase of recovery time appeared after iontophoresis. Comparison between epinephrine effect and Ca and Na ions and combination of Na with epinephrine indicated significant different (* = $P < 0.05$).

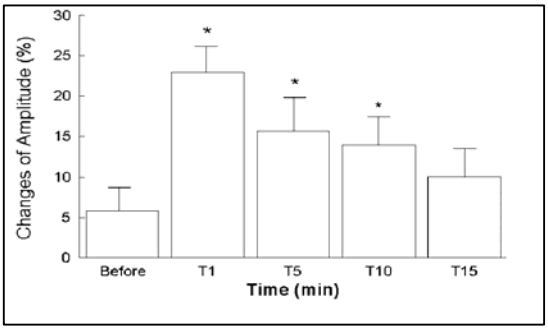

Fig. 7. Mean ± SD of percentage difference between fifth and first amplitudes of CMAP in normal group by repetitive nerve stimulation test. After iontophoresis of epinephrine at one (T1), five (T5) and ten (T10) minute later in comparison to before the mean of increment finding were significant (* = $P < 0.05$).

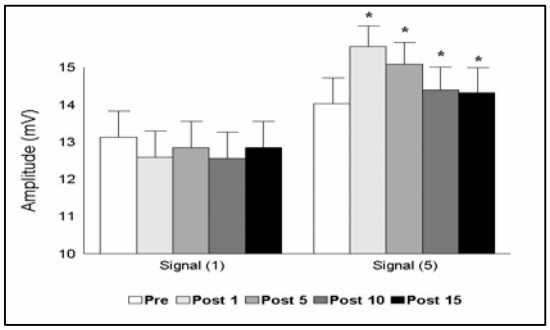

Fig. 8. Mean ± SD of amplitudes of first and fifth compound muscle action potentials (CMAPs) (signal) at before (pre) and after (post) iontophoresis of epinephrine in normal group. In comparison to first signal, amplitudes of fifth signal increased significantly after (post) iontophoresis (* = $P < 0.05$).

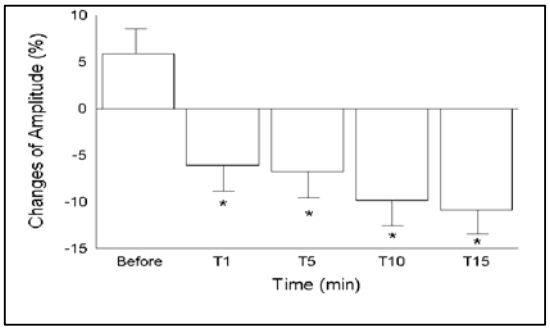

Fig. 9. Mean ± SD of percentage difference between fifth and first amplitudes of CMAP in patients with myasthenia gravis by RNS test. Mean of decrement significantly decreased after iontophoresis of epinephrine at one (T1), five (T5), ten (T10) and fifteen (T15) minutes later (* = $P < 0.05$).

Table 1. Mean (SD) of time dependent specifications of CMAP following iontophoresis of different ions (msec)

Time	Agents	Depolarization	Repolarization	Recovery
Before	Sodium chloride	3.32 (0.88)	2.60 (0.44)	3.13 (0.71)
	Gluconate calcium	2.76 (0.40)	2.61 (0.32)	2.57 (0.72)
	Epinephrine	4.35 (0.99)	2.47 (0.41)	3.86 (1.13)
	Epinephrine and sodium chloride	3.90 (0.67)	2.84 (0.36)	3.66 (1.25)
	Distilled Water	3.76 (1.02)	2.94 (0.48)	4.20 (1.22)
T1	Sodium chloride	3.86 (0.75)*	3.21 (0.46)*	13.35 (3.82)*
	Gluconate calcium	3.59 (0.42)*	2.90 (0.45)	18.42 (5.26)*
	Epinephrine	4.93 (0.98)*	2.71 (0.42)	5.65 (2.62)
	Epinephrine and sodium chloride	4.42 (0.98)	3.24 (0.40)	15.89 (8.54)*
	Distilled Water	3.58 (0.81)	3.38 (1.00)	5.55 (2.97)
T5	Sodium chloride	3.96 (0.70)*	2.93 (0.34)*	11.23 (3.82)*
	Gluconate calcium	3.80 (0.61)*	2.77 (0.55)	16.34 (6.21)*
	Epinephrine	4.88 (0.96)*	2.63 (0.43)	4.72 (2.10)
	Epinephrine and sodium chloride	4.48 (0.97)*	3.01 (0.35)	13.76 (7.92)*
	Distilled Water	3.64 (0.80)	3.23 (0.79)	4.78 (2.56)
T10	Sodium chloride	3.88 (0.69)*	2.82 (0.43)*	10.02 (4.31)*
	Gluconate calcium	3.79 (0.43)*	2.71 (0.50)	12.88 (5.78)*
	Epinephrine	4.84 (0.98)*	2.62 (0.37)	4.04 (1.04)
	Epinephrine and sodium chloride	4.56 (0.89)*	2.87 (0.26)	11.86 (7.28)*
	Distilled Water	3.60 (0.76)	3.15 (0.70)	4.45 (2.23)
T15	Sodium chloride	3.98 (0.75)*	2.79 (0.47)	7.93 (4.45)*
	Gluconate calcium	3.95 (0.52)*	2.87 (0.50)	13.06 (5.96)*
	Epinephrine	4.78 (1.04)*	2.58 (0.38)	4.04 (1.04)
	Epinephrine and sodium chloride	4.55 (0.89)	2.96 (0.31)	9.29 (5.43)
	Distilled Water	3.67 (0.86)	3.15 (0.54)	3.98 (1.38)

*Significant different between before and after iontophoresis ($P < 0.05$).

Table 2. Mean (SD) of slopes of CMAP following iontophoresis of different ions (mV/msec)

	Agents	Depolarization	Repolarization	Recovery
Before	Sodium chloride	2.23 (1.15)	4.53 (1.20)	1.95 (0.50)
	Gluconate calcium	2.21 (1.15)	4.77 (1.75)	2.70 (0.81)
	Epinephrine	3.86 (1.13)	7.62 (1.89)	2.37 (0.82)
	Epinephrine and sodium chloride	1.67 (0.87)	4.37 (0.98)	1.82 (0.77)
	Distilled Water	2.15 (0.45)	5.51 (1.29)	2.23 (1.51)
T1	Sodium chloride	1.22 (0.51)*	3.26 (1.33)*	0.45 (0.21)*
	Gluconate calcium	1.63 (0.56)	4.72 (1.36)	0.46 (0.25)*
	Epinephrine	1.94 (0.60)	7.03 (1.87)	1.94 (0.90)
	Epinephrine and sodium chloride	1.41 (0.87)	4.27 (0.98)	0.86 (0.85)*
	Distilled Water	1.76 (0.34)	4.55 (1.26)*	1.91 (1.09)
T5	Sodium chloride	1.24 (0.55)*	3.59 (1.36)*	0.60 (0.38)*
	Gluconate calcium	1.63 (0.46)	5.17 (1.82)	0.63 (0.53)*
	Epinephrine	2.01 (0.67)	7.38 (2.49)	2.26 (0.98)
	Epinephrine and sodium chloride	1.48 (0.72)	4.57 (0.93)	0.90 (0.88)*
	Distilled Water	1.89 (0.36)	4.86 (1.36)	2.17 (1.25)
T10	Sodium chloride	1.35 (0.59)*	3.81 (1.30)*	0.72 (0.53)*
	Gluconate calcium	1.67 (0.61)	5.26 (1.99)	0.99 (1.16)*
	Epinephrine	2.01 (0.59)	7.52 (2.60)	2.52 (0.86)
	Epinephrine and sodium chloride	1.53 (0.68)	4.83 (0.88)	1.01 (0.94)*
	Distilled Water	1.96 (0.36)	4.98 (1.38)	2.28 (1.38)
T15	Sodium chloride	1.43 (0.65)*	4.06 (1.43)	1.02 (0.77)*
	Gluconate calcium	1.55 (0.55)	4.81 (1.66)	0.97 (1.12)*
	Epinephrine	2.00 (0.47)	7.48 (2.19)	2.79 (1.09)*
	Epinephrine and sodium chloride	1.58 (0.70)	4.71 (0.82)	1.13 (0.91)*
	Distilled Water	1.95 (0.39)	4.90 (1.28)	2.30 (1.14)

*Significant different between before and after iontophoresis ($P < 0.05$).

DISCUSSION

Iontophoresis of active ions (sodium and calcium) increased depolarization, recovery and duration times of CMAPs. Also these ions reduced slope of depolarization and recovery stages. These findings are due to hyperpolarization properties that were produced by electrical field of direct current. Epinephrine increased time of depolarization of CMAP, but this increase was very small in comparison to other ions; iontophoresis application of epinephrine also increased slope of recovery stage. Iontophoresis of epinephrine in normal subjects caused a greater increase in Na^+-K^+ active transport stage in comparison to active ions such as sodium and calcium. These findings indicate that epinephrine can induce contractility of muscle fibers by iontophoresis. Clausen *et al.* have shown that adrenoceptors which are active in pre and postsynaptic regions and also beta adrenoceptors for potentiation of Na^+/K^+ pump are sensitive to adrenaline on muscle fibers (7, 8).

In contrast to these findings, positive ions that are increased at sites of neuromuscular junction or muscle fibers following iontophoresis can hyperpolarize them and depolarization time is increased by iontophoresis of sodium and calcium ions. Also this effect reduced speed of activity of Na-K pump. Combination of electrical effects (positive ions transfer and increase of concentration near of nerve and muscle) of iontophoresis of epinephrine with 50 mA.min in normal subjects increased amplitudes of fifth CMAP in low repetition stimulus test, and caused increase of

percentage of amplitude differences. These effects correspond to Clausen studies in presence of specific receptors for epinephrine and norepinephrine on post- synaptic membrane in neuromuscular junction to active Na-K transport (7, 8). Depression of percentage difference of amplitude of fifth to first CMAP in patients with myasthenia gravis disease (long term treatments) with normal findings in neuromuscular junction in pre test, following iontophoresis of epinephrine, indicate that these patients have sensitive neuromuscular membranes to epinephrine. Sensitivity to iontophoresis of epinephrine in these patients is important and this specification in clinical electroneurography is useful. In addition, combination of iontophoresis of epinephrine with other electroneurophysiological tests such as low repetition stimulus test is a new protocol and if improved with other effective drugs can be useful to assess of neuromuscular functions.

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