

The evaluation of the therapeutic effect of memantine in sepsis induced critical illness polyneuropathy

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ÖZET

Memantin' in sepsis indükte kritik hastalık polinöropatisindeki terapötik etkilerinin incelenmesi

AMAÇ: Çalışmamızın amacı, sıçanlarda cerrahi olarak geliştirilen sepsis indükte kritik hastalık polinöropatisindeki memantin farklı dozlarıdaki etkilerini, elektromiyografi (EMG) bulgularından birleşik kas aksiyon potansiyelleri (BKAP), distal latans gibi EMG bulguları ve plazma tümör nekrotizan faktör - α (TNF- α) ve malonedialdehit (MDA, plazma lipit peroksidaz göstergesi) seviyeleri eşliğinde incelemektir.

METOD: Çalışma gruplarımız beş grup olarak belirledik, 24 sıçana çekal ligasyon ve delme işlemi uygulanarak sepsis geliştirildi. Gruplar; 1: normal, 2: sham grubu (sadece periton açılıp kapatıldı), 3: tedavi verilmeyen sepsis grubu, 4: sepsis + 15 mg/kg memantin verilen, 5: sepsis+ 30 mg/kg memantin grubu olarak belirlendi. Tüm gruplara EMG yapılarak plazma MDA ve TNF- α seviyeleri ölçüldü.

BULGULAR: Plazma MDA ve TNF- α seviyeleri tüm çekal ligasyon ve delme işlemi uygulanan sıçanlarda istatistiksel olarak anlamlı derecede artmıştı, ek olarak tüm sepsis gruplarında distal latanslar istatistiksel olarak uzamış, BKAP amplitüdüler küçülmüştü. Hem 15 mg/kg hem de 30 mg /kg dozlarında verilen memantin gruplarında plazma MDA ve TNF- α seviyeleri istatistiksel olarak anlamlı derecede azalmıştı, ayrıca bu gruplarda BKAP amplitüdüler istatistiksel olarak artmış, distal latanslar kısalmıştı.

SONUÇ: Biz çalışmamızda memantin sepsis indükte kritik hastalık polinöropatisindeki antioksidan ve

nöroprotektif etkilerini plazma MDA ve TNF- α seviyelerini azaltmak suretiyle olduğunu gözlemledik.

Anahtar sözcükler: Kritik hastalık nöropatisi, memantin, elektromiyografi, malonedialdehit, tümör nekrotizan faktör - α

ABSTRACT

OBJECTIVES: The purpose of our study is to investigate the effects of the different dosage of memantine for the treatment of Critical Illness Polyneuropathy (CIP) in rats that have surgically induced sepsis, by using electromyography (EMG) signs, such as amplitude and duration of compound muscle action potentials (CMAP), distal latency, and by using levels of plasma tumor necrosis factor (TNF)- α and lipid peroxides (malondialdehyde, (MDA)).

METHODS: Rats were divided into five groups and cecal ligation and puncture (CLP) procedure was performed on 24 rats. Study groups were designed as follows: Group 1: normal (control, n=6); Group 2: sham-operated (n =6); Group 3: CLP (untreated group, n = 8); Group 5: CLP and 15 mg/kg memantin (n = 8); Group 6: CLP and 30 mg/kg memantin (n = 8). EMG was performed and plasma MDA and TNF- α levels were evaluated in all groups.

RESULTS: Our findings showed an increase at the plasma levels of TNF- α and MDA in cecal ligation and puncture group. Besides, we established a reduction in CMAP amplitude and prolongation of distal latency in CLP group. Administration of 15 and 30 mg/kg Memantine significantly provided a decrease in TNF- α and MDA levels in CLP group. CMAP distal latency was reduced in

all memantine-treated groups.

CONCLUSION: We observed that memantine showed its antioxidant and neuroprotective effects by decreasing the plasma MDA and TNF- α levels in CIP.

Key words: Critical illness polyneuropathy; memantine; electromyography; malondialdehyde, tumor necrosis factor- α

INTRODUCTION

Critical illness polyneuropathy (CIP) was first described by Bolton and colleagues in 1986.¹ CIP often appears as a generalized neuromuscular weakness and paresis. This kind of polyneuropathy usually occurs in patients who are admitted to intensive care units (ICU) and it is observed in critically ill patients with sepsis or multi-organ failure. CIP may occur in the first week after intubation or in between second and fifth days if the presence of sepsis is proven. Clinical features of CIP are predominantly distal tetraparesis or tetraplegia, weakness of the respiratory muscles, reduced or absent deep tendon reflexes, loss of pain, temperature and vibration sense.² Commonly, CIP affects the lower limbs more than the upper limbs. In addition, occasionally weaning failure from mechanical ventilation is the first manifestation of diagnosis.³⁻⁵ Approximately 70% of the patients in sepsis or with systemic inflammatory response syndrome (SIRS) will develop CIP.⁶ In between 49% to 77% of the ICU patients who are at least hospitalized for seven days have the diagnosis of CIP.⁷⁻⁸

The gold standard used for the diagnosis of CIP is nerve conduction studies. The first electrophysiological sign is the reduction in amplitude of the sensory and compound muscle action potentials (CMAP) indicating an axonal sensorimotor polyneuropathy.⁹ Progressive tissue damage, organ dysfunction and infection affecting the microcirculation and also endoneurial edema developing through activation of proinflammatory cytokines causing distal axonal degeneration and hypoxia are responsible for the pathogenesis of CIP.¹⁰

Supportive treatments including nutritional interventions, supplements and anti-oxidant therapies, growth hormones and immunoglobulins were proposed to manage the muscle weakness in critically ill patients.¹¹ Neuromuscular blocking agents and corticosteroids should be used at minimal doses and for a period as short as possible.¹² Insulin reduces the enhanced permeability of capillaries; prevents the passage of neurotoxic factors into the endoneurium.¹³

Glutamate is one of the main neurotransmitters in the brain and it is known that in response to injury glutamate release increases. Glutamate is known to be excitotoxic for the neural tissue. Excitotoxicity is defined as uncontrolled release of glutamate, the activation of NMDA receptors, and membrane depolarization causing excessive passage of Ca, Na and H₂O molecules into the cell.¹⁴ Ca flow into neurons may activate the neuronal nitric oxide (NO) synthase. This causes the increase of NO reacting with superoxide anion triggering toxic peroxynitrite. As a result peroxynitrite causes severe damage of the cell.¹⁵ It is believed that the increase of Ca level is the major component of the cell death.

Memantine (1-amino-3,5-dimethyladamantane hydrochloride) is an NMDA receptor antagonist and it is used in many neurological disorders such as Alzheimer's disease and Parkinson disease. Memantine shows its effect by reducing the glutamatergic neuronal damage. Therefore, Memantine is used as an antioxidant in some ischemic events.

Regarding to these informations, we thought whether memantine would have therapeutic effects on experimentally induced CIP model in rats or not. In our study, we evaluated the electrophysiological findings, the changes in the plasma TNF- α levels, in MDA levels of surgically induced sepsis in rats, and the effects of different doses of memantine treatment on CIP by performing electrophysiology, plasma TNF- α , and MDA levels.

MATERIALS AND METHODS

Animals

In this study 45 male Sprague Dawley albino mature rats, weighing 200–250 g, were used. Animals were fed ad libitum and housed in pairs, in steel cages having a temperature-controlled environment (22 \pm 2 °C) with 12-h light/dark cycles. The experimental procedures were approved by the Committee for Animal Research of Gaziosmanpaşa University (Approval number: 2013-HADYEK 30). All animal studies are strictly conformed to the animal experiment guidelines.

Experimental procedures

Rats were randomly assigned into five groups and cecal ligation and puncture (CLP) procedure was performed on 33 rats to induce a sepsis model. 9 rats died during the first 24 h following surgical procedure and were excluded from the study. There was no mortality in the

sham-operated group. Study groups were designed as follows: Group 1: normal (nonoperative and orally fed control group, n=6); Group 2: sham-operated (n =6); Group 3: CLP (untreated group, n = 8); Group 4: CLP and 15 mg/kg memantin intraperitoneal (i.p.) (n = 8); Group 5: CLP and 30 mg/kg memantin i.p.(n=8). For the surgical procedure, rats were anesthetized by intraperitoneal injection of a combination of ketamine hydrochloride at a dose of 80 mg/kg and 7 mg/kg xylazine hydrochloric (Alfazyne; Alfasan International BV, Woerden, Holland).

Under aseptic conditions, a 3 cm midline laparotomy was performed to allow exposure of the cecum with the adjoining intestine. The cecum was ligated tightly with a 3.0 silk suture at its base under the iliocolic valve and punctured once with a 22-gauge needle. The cecum was then gently squeezed to extrude a small amount of feces from the perforation site. The cecum was put back to its location in the peritoneal cavity, and the laparotomy incision was closed with 4-0 polyglactin 910 sutures. Following the surgery, after the recovery period, animals were placed in their cages. In the sham group, under aseptic conditions, only laparotomy was performed on rats, but their cecum was neither ligated nor punctured. In this model, rats were accepted as septic 5 h following CLP.¹⁶ All treatments were performed within the first hour of the surgical procedure.

Measurement of plasma TNF- α levels

Plasma TNF- α levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kit (Biosciences). The plasma samples were diluted 1:2 and TNF- α was determined in duplicate according to the manufacturer's guide. The detection range for TNF- α assay was <2 pg/ml.

Measurement of lipid peroxidation

Lipid peroxidation was determined in plasma samples by measuring malondialdehyde (MDA) levels as thiobarbituric acid reactive substances (TBARS). Briefly, trichloroacetic acid and TBARS reagent were added to the plasma samples, then mixed and incubated at 100 °C for 60 min. After cooling on ice, the samples were centrifuged at 3000 rpm for 20 min and the absorbance of the supernatant was read at 535 nm. MDA levels were expressed as nM and tetraethoxypropane was used for calibration.¹⁷

Electrophysiological recordings

EMG studies were performed 36 h after surgery. EMG data were obtained three times from the right sciatic nerve stimulated supramaximally (intensity 10 V, duration 0.05 ms, frequency 1 Hz, in the range of 0.5-5000 Hz, 40 kHz/s with a sampling rate) by a Medelec-Oxford Synergy bipolar subcutaneous needle stimulation electrode from the sciatic notch.

CMAPs were recorded from 2-3 interosseous muscles by unipolar platinum electrodes. Data were evaluated using Medelec-Oxford Synergy Quantitative EMG Test Software with distal latency and amplitude of CMAP being the parameters. During the EMG recordings, rectal temperatures of the rats were monitored by a rectal probe (HP Viridia 24-C; Hewlett-Packard Company, Palo Alto, CA) and the temperature of each rat was kept at approximately 36 -37 °C by heating pad. Following EMG recordings, animals were euthanized and blood samples were collected by cardiac puncture for biochemical measurements. They were centrifuged at 3000 rpm for 10 min at room temperature and stored at -20 °C until assay.

Statistical analysis

Statistical evaluation was performed using SPSS version 15.0 for Windows. The groups of parametric variables were compared using the Student's t test and analysis of variance. Also, the groups of nonparametric variables were compared using the Mann-Whitney U test. In addition, the Shapiro-Wilk test was used for parametric-non-parametric differentiation. Results are presented as mean+SEM. A p < 0.05 was accepted as statistically significant.

RESULTS

Assesment of Plasma TNF- α Levels

CLP group demonstrated a significant increase in plasma levels of TNF- α compared with the normal control and the sham-operated rats (251.8 \pm 13.3 pg/ml, 20.5 \pm 3.1 pg/ml, 26.1 \pm 1.03 pg/ml, respectively; p<0.0001). Administration of 15 and 30 mg/kg Memantine significantly provided a decrease in TNF- α levels in CLP group (167.08 \pm 6.5 pg/ml and 169.7 \pm 6.9 pg/ml, respectively; p < 0.0001). However, there was no statistical difference between 15 mg/kg Memantine-treated group and 30 mg/kg Memantine-treated group in terms of plasma levels of TNF- α (>0,05) (**Fig 1**).

Assesment of Plasma MDA Levels

Malondialdehyde (MDA) levels were found to be significantly higher in the CLP group than the normal control and the sham-operated groups (204.7 ± 14.6 nM, 61.8 ± 4.3 nM, 65.9 ± 4.8 nM, respectively; $p < 0.05$). Administration of 15 and 30 mg/kg Memantine significantly triggered a decrease of MDA levels in CLP groups (164.2 ± 7.3 nM and 130.7 ± 8.05 nM, respectively; $p < 0.001$). There was a statistical significant difference between the 15 mg/kg Memantine-treated group and 30 mg/kg Memantine-treated group in terms of the plasma levels of MDA. More significant reduction was detected in 30 mg/kg Memantine-treated group than 15 mg/kg Memantine-treated group in terms of plasma levels of MDA ($p < 0.001$) (**Fig 2**).

Electrophysiological Findings

Highly significant reduction was found in CMAP amplitude in CLP group compared with the normal control and sham-operated groups (4.2 ± 0.19 mV, 9.29 ± 0.28 mV and 8.9 ± 0.4 mV, respectively; $p < 0.0001$). CMAP amplitude was significantly improved in 15 mg/kg Memantine-treated and 30 mg/kg Memantine-treated groups (6.9 ± 0.25 mV and 8.08 ± 0.33 mV, respectively ($p > 0.0001$)). CMAP distal latency meaningfully was prolonged in the CLP group compared with normal control and sham-operated groups (3.8 ± 0.08 ms, 2.53 ± 0.04 ms and 2.58 ± 0.02 ms, respectively; $p < .0001$). CMAP distal latency was reduced in all Memantine-treated groups ($p < 0.0001$). However, there was no statistical difference between 15 mg/kg Memantine-treated group and 30 mg/kg Memantine-treated group in terms of CMAP distal latency ($p > 0.05$) (**Fig 3-4**).

DISCUSSION

Critical illness polyneuropathy is a sensorimotor axonal polyneuropathy that is usually detected in patients hospitalized in the intensive care unit for a week or in patients with MOF, Systemic Inflammatory Response Syndrome (SIRS) or sepsis.¹⁸ CIP is a common issue in intensive care units and the clinical syndrome consists of generalized flaccid weakness prominent in the distal limbs and reduction or loss of deep tendon reflexes. CIP can be seen at any age, but men are effected more than women. CIP is considered to be a complication of systemic inflammatory response triggered by conditions such as sepsis. Mononuclear cells play a large role in releasing of conventional proinflammatory cytokines such as interleukin 1 (IL-1), IL-6 and TNF- α . TNF- α ; by activating leukocyte surface adhesion molecules

causes adhesion of neutrophils to endothelial cells. As a result of degranulation of activated neutrophils, released proteases and toxic oxygen radicals facilitates damaging of endothelial cells. Finally, sepsis causes membrane excitability in ischemic cells, and by this polyneuropathy occurs.

It is observed that excitator aminoacids (EAA) spreading through the synaptic gap have reached neurotoxic levels in ischemic neuronal cell culture studies. Glutamate is the most well-known one among the EAA and this damage can be moderated by NMDA antagonists which is the one of the glutamate receptors.¹⁹⁻²⁰

Memantine is a non-competitive NMDA receptor antagonist and it has been shown that it has protective effects on neuronal death in transient frontal brain ischemia,²¹ hypoxic cerebral ischemia,²² spinal cord ischemia,²³ and retinal ischemia²⁴ in animal studies. It is demonstrated that giving continous Memantine infusion in Alzheimer disease protects the hippocampal CA1 neurons from the effects of neurodegeneration in the study on Danysz et al..²⁵

The effects of Memantine on plasma MDA and TNF- α levels and EMG findings have been investigated in rats with sepsis in our study. We determined that Memantine decreases significantly TNF- α levels which increased in rats in sepsis. TNF- α is the most important cytokine which plays role in natural immune system and it is released from macrophages and T lymphocytes. In addition, TNF- α is responsible for the systemic complications in serious infections. Also, experimentally giving TNF- α to animals causes the clinical symptoms which are seen in sepsis.²⁶ TNF- α demonstrates its effect by activating nitric oxid syntetase enzyme.²⁷ NO is the most fundamental substance which is responsible for vasodilatation in sepsis.²⁸ Furthermore, one of the mediators being responsible for inflammatory response is free oxygen radicals (FOR).²⁹ FORs deteriorate cell membrane by causing lipid peroxidation and inhibiting mitochondria ATP syntesis. This leads to oxidative damage of DNA and proteins. Different kinds of experiments and clinical studies have been carried out with antioxidant agents to prevent free oxygen increase being caused by sepsis. As an indirect sign of FORs, MDA levels (the last production of lipid peroxidation that is revealed at the end of damage) can be used. In our study, plasma MDA levels have increased dramatically in CLP group and it is determined that MDA levels have decreased significantly in Memantine-treated groups.

The best method for the diagnosis of CIP is

electrophysiologic studies. Axonal polyneuropathy appears by the reduction in CMAP and sensory action potential amplitudes.³⁰⁻³² Fibrillation potentials, denervation potentials and positive sharp waves may be observed after two or three weeks following clinical symptoms.³³⁻³⁴

Although the CIP pathophysiology in sepsis is not certainly known, it is stated that the increasing of permeability of small endoneurial vessels, endoneurial edema and increasing toxic factor penetration have a role in CIP pathophysiology. Membrane depolarization in motor axons lead to CIP development related to endoneurial hyperkalemia and hypoxia.³⁵ As in the previous study, a decrease has been detected in CMAP amplitude and an increase has been detected in distal latency in rats with CLP in our study^{30-31,36}. Furthermore, increase in CMAP amplitudes and decrease in latency in Memantine-treated groups were detected. It is seen that Memantine (the antagonist of NMDA receptors) decreases the neurotoxicity related to glutamate and the influence of antioxidant in many studies.³⁷⁻³⁸

Consequently, antioxidant effect of Memantine has been shown by decreasing plasma MDA and TNF- α levels in CIP. Meanwhile, it showed a neuroprotective effect by improving in EMG findings. Nonetheless, more studies are necessary to support the routine use of Memantine and to show its antioxidant and neuroprotective effects.

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Figure 1: TNF- α levels are represented for each group. In CLP group, TNF- α levels are higher than normal and sham operated group. TNF- α levels reduced in 15 mg/kg and 30 mg/kg Memantine-treated groups in rats.

Figure 2: MDA levels are represented for each group. In CLP group, MDA levels are higher than normal and sham operated groups. MDA levels reduced in 15 mg/kg and 30 mg/kg Memantine-treated groups in rats.

Figure 3: Electrophysiological findings in CMAP amplitude and CMAP distal latency in normal group, sham group, CLP and Memantine-treated groups in rats.

Figure 4: Samples of CMAP recorded from (A) Normal group, (B) Sham group, (C) CLP group, (D) CLP and 30 mg/kg memantin.

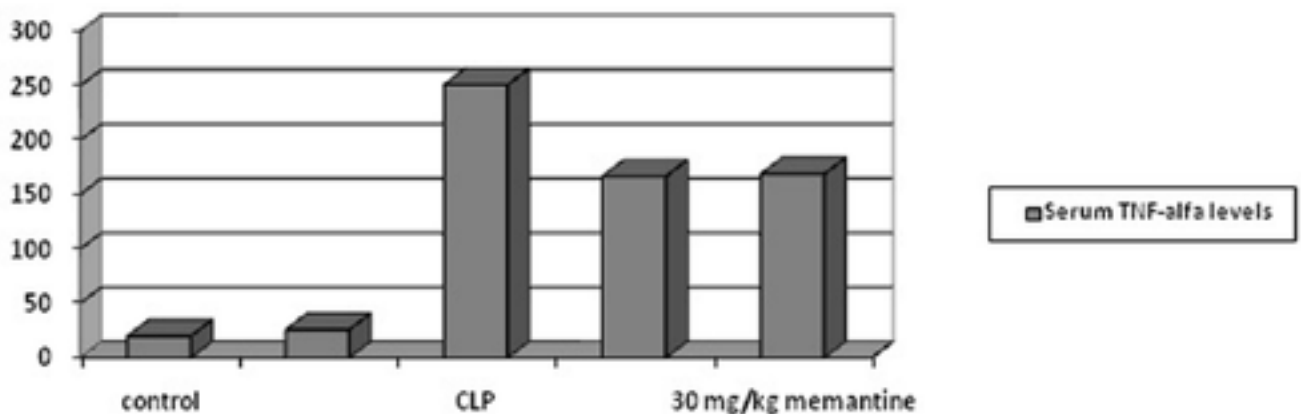


Figure 1

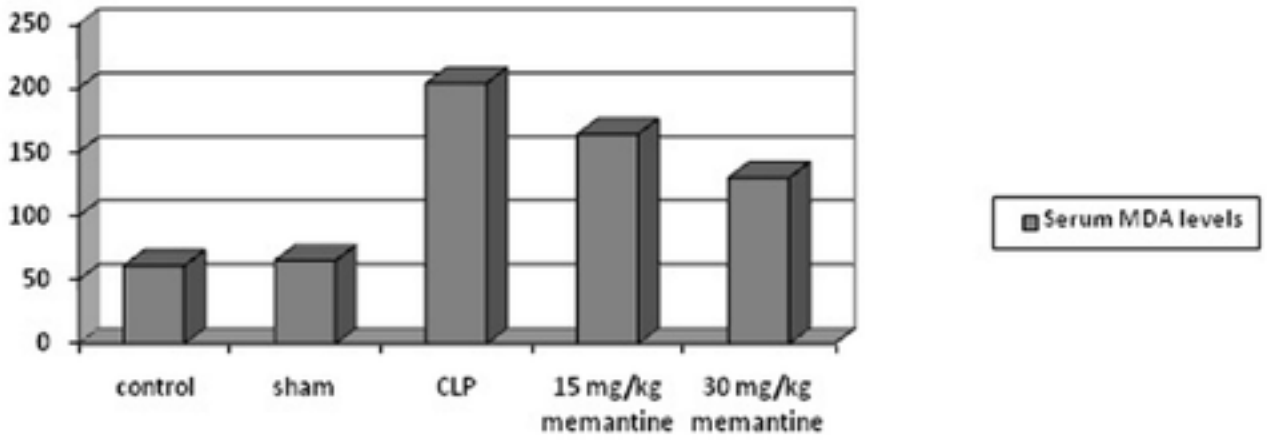


Figure 2

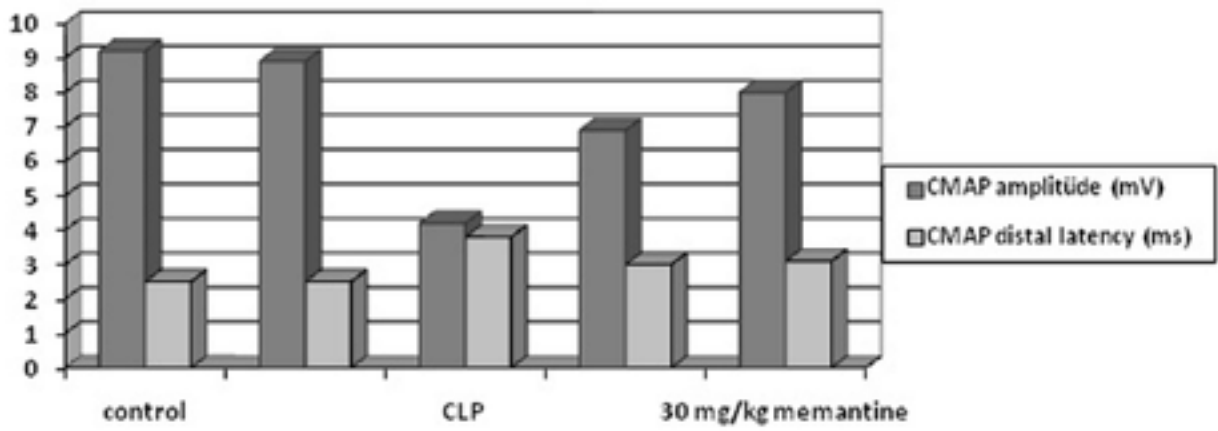


Figure 3

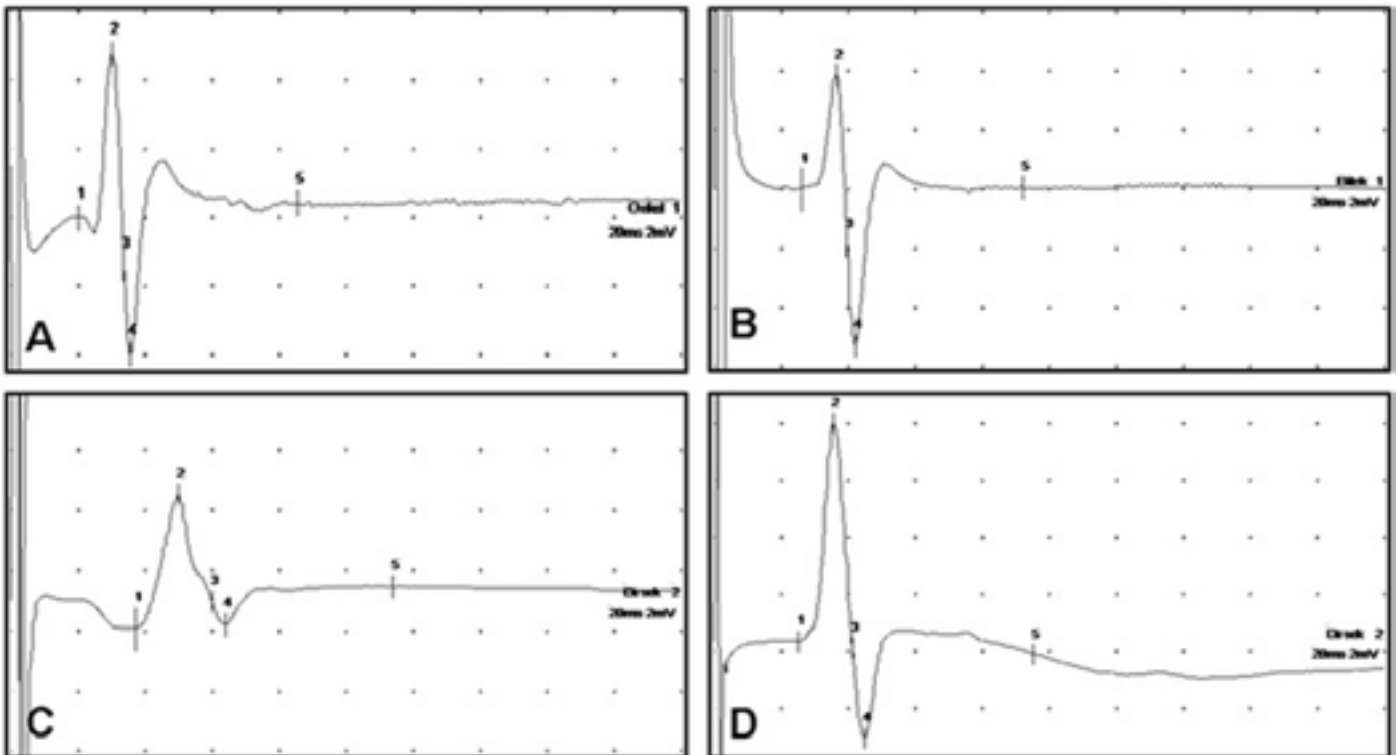


Figure 4