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Deneysel Çalışma

Effects of IgM-enriched immunoglobulin and fluid replacement on nerve conduction velocity in experimental sepsis

Deneysel sepsiste IgM ile zenginleştirilmiş immünglobulin ve sıvı replasman tedavisininin sinir ileti hızına olan etkileri

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BACKGROUND

Neuromuscular abnormalities in sepsis, termed critical illness polyneuropathy (CIP), have been suggested to be induced by inflammatory mechanisms and/or relative hypovolemia. CIP is characterized by early electrophysiological findings before the clinical symptoms. This study aimed to investigate the effect of intravenous immunoglobulin (IVIG) and volume replacement therapies on the possible nerve conduction velocity (NCV) alterations in the early phase of experimental sepsis.

METHODS

Forty-six Sprague-Dawley rats were randomly assigned to four groups. Cecal ligation/perforation was performed to induce experimental sepsis. NCV was assessed in the tail nerve.

RESULTS

There was no statistically significant difference in NCV levels within and among the Sham-operated, colloid- and IVIG-treated groups. In the sepsis without treatment group, there was a statistically significant decrease in NCV levels.

CONCLUSION

NCV is decreased in the early stage of experimental sepsis and it may be accepted as an early electrophysiological sign in CIP. Treatment with either IgM-enriched IVIG or early volume replacement appears to prevent the decrease in NCV in the early phase of experimental sepsis. Results were statistically indistinguishable between the IVIG- and colloid-treated groups. No statistical difference between these groups is noteworthy. There is a need to clarify the mechanisms of action with further randomized, clinical and experimental trials.

Key Words: Experimental study; fluid replacement; immunoglobulin; nerve conduction velocity; sepsis.

AMAÇ

Sepsiste yoğun bakım polinöropatisi (YBP) olarak adlandırılan nöromusküler ileti bozukluklarının erken dönemde enflamatuvar mekanizmalar ve/veya rölatif hipovolemi ile tetiklendiği ileri sürülmektedir. YBP, klinik bulgulardan önce erken dönemde beliren elektrofizyolojik bulgularla kendini gösterir. Çalışmamızda, IVIG ve volüm replasman tedavisinin deneysel sepsisin erken fazında görülebilen sinir ileti hızındaki (SİH) değişikliklere olan etkisinin araştırılması amaçlandı.

GEREÇ VE YÖNTEM

Randomize olarak 46 Spraque-Dawley sıçan çalışmaya dahil edildi. Deneysel sepsis çekal ligasyon ve perforasyon ile oluşturuldu. SİH, kuyruk sinirindeki ölçümlerle değerlendirildi.

BULGULAR

Sham grubu, kolloid grubu ve IVIG grubunda hem grup içinde hem de gruplar arasında SİH'nın değişimi açısından anlamlı fark olmadığı görüldü. Herhangi bir tedavinin uygulanmadığı sepsis grubunda ise; SİH'nın başlangıç değerine göre anlamlı azaldığı görüldü.

SONUÇ

YBP'nin erken elektrofizyolojik bir bulgusu olarak kabul edilebilen SİH sepsisin erken döneminde azalmaktadır. Deneysel sepsisin erken döneminde görülen SİH'deki azalmanın IgM ile zenginleştirilmiş IVIG verilmesi ile veya erken yapılan volüm replasmanı ile önlenebileceği görülmektedir. IVIG tedavisi uygulanan grupla kolloidle erken volüm replasmanı uygulanan grup arasındaki sonuçların istatistiksel olarak farklı olmaması dikkat çekici olarak değerlendirilmiş ve konu ile ilgili mekanizmanın açığa çıkması için randomize klinik ve deneysel çalışmalara ihtiyaç olduğu kanısına varılmıştır.

Anahtar Sözcükler: Deneysel çalışma; sıvı replasmanı; immunoglobulin; sinir ileti hızı; sepsis.

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Neuromuscular abnormalities seen in patients with sepsis and multiple organ failure (MOF) were first described as CIP (critical illness polyneuropathy) by Bolton et al. in 1984.[1-4] Neuromuscular transmission deficits observed in systemic inflammatory response syndrome (SIRS) and sepsis are thought to develop due to the inflammatory responses facilitated by infection and trauma and microcirculation deficits.

Most of the electrophysiological studies accepted to be useful in the early prognosis are principally related with amplitude, latency and duration. The decrease in compound muscle action potential (CMAP) amplitude and the increase in latency are the first electrophysiological findings before the clinical symptoms appear.[4-6] There are a limited number of clinical studies in which nerve conduction velocity (NCV) was measured, but none of these studies was performed in the early phase of sepsis,[7,8] and there is no data to date showing electrophysiological studies and NCV searched experimentally in sepsis.

Recently, these neuromuscular conduction disorders were thought to be induced by inflammatory mechanisms and are accepted as a neurological involvement of sepsis. In addition, administration of intravenous immunoglobulin (IVIG) treatment for immunomodulation therapy in sepsis has shown promising results in the autoimmune polyneuropathies.[9-13] Especially IgM-enriched polyclonal IVIG compounds are accepted as having potent immunomodulatory effects in the inflammatory processes.[14] In the literature, most of the researches done on the treatment of sepsis with IVIG generally aimed to evaluate the beneficial effects on the clinical survey and prognosis. However, there has been no experimental research reported on the effect of early IVIG treatment on the neuromuscular transmission disorder in sepsis.

On the other hand, because of the end-organ oxygenation failures due to the microcirculation deficit facilitated by relative or absolute hypovolemia in sepsis, all the organs begin to deteriorate. Since the nervous system, the most vulnerable tissue to hypoxia, is affected first, it is crucial to maintain effective fluid resuscitation and adequate intravascular volume in the early phases of sepsis in order to minimize or prevent end-organ deficits.

In this study, we researched the effect of early administration of IgM-enriched IVIG and volume replacement on the probable alterations in NCV in the early phase of sepsis.

MATERIALS AND METHODS

After Animal Ethics Committee approval, the study was conducted in the Research Laboratory of the Department of Anesthesiology and the Intensive Care Unit (ICU) in Ege University Faculty of Medicine.

Experimental Procedures

Forty-six adult male Sprague-Dawley rats aged 2-3 months and weighing approximately 318.86±47.90 g were used. All the rats were housed in cages in an acclimatized room at standard room temperature with l2 hr light/dark cycles one week before the experiments. Rats were allowed free access to water and standard chow. All rats were randomly divided into four groups:

Group I (n=10) (Sham Group): Sham operated.

Group II (n=12) (Colloid Group): Cecal ligation and puncture (CLP) operated + Colloid- treated with Gelatina Succinilada (Gelofusine, Braun, Germany) (IV 5 ml/kg).

Group III (n=12) (IVIG Group): CLP operated + IgM-enriched polyclonal IVIG preparation treated with Pentaglobin (Biotest Pharma GmbH, Dreieich, Germany) (IV 5 ml/kg).

Group IV (n=12) (Untreated Sepsis Group): CLP operated + no treatment.

Colloid solution therapy and IVIG therapy were infused in the first hour after CLP. IVIG therapy was administrated only as a single dose since we aimed to determine the effect of early administration of IgM-enriched IVIG and volume replacement on the probable alterations in NCV in the early phase of sepsis (in the first 24 hours).

For surgical interventions, rats were anesthetized using ketamine (80 mg/kg) and xylazine (10 mg/kg), via intraperitoneal (ip) route.

Sepsis was induced by CLP performed by the procedure described previously.[15,16] 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 below the ileocecal valve, perforated once with a 22-gauge needle, and gently squeezed to extrude a small amount of feces from the perforation site. After returning the cecum in to the peritoneal cavity, the laparotomy incision was closed with 4.0 silk sutures. In this sepsis model, rats are accepted as septic five hours after CLP.

In the sham-operated group, only laparotomy was performed and cecum of the rats was neither ligated nor punctured.

Electrophysiological Techniques

Electrophysiological recordings were obtained from the tail nerve stimulated supramaximally (intensity 10 V, duration 0.1 ms, frequency 1 Hz) by bipolar surface stimulation electrode, and compound nerve action potentials (CNAP) were recorded by means

Table 1. NCV measurements

Groups	NCV (m/s)			
	Preoperative	6th hour	12th hour	24th hour
Sham Group (n=10)	26.01±7.36	26.20±7.78	27.80±9.23	28.45±6.24
Colloid Group (n=12)	25.61±4.45	21.99±5.42	25.70±6.49	25.62±5.10
IVIG Group (n=12)	26.71±4.13	25.13±8.66	27.07±5.10	24.46±5.85
Untreated Sepsis Group (n=12)	30.12±7.83	21.86±5.32*	25.70±7.87	22.86±5.20*

All values are mean ± SD for each group. (*p<0.05).

Table 2. Change of NCV (%)

Groups	Preoperative (%)	6th hour (%)	12th hour (%)	24th hour (%)
Sham Group (n=10)	100.00	2.05±20.14	11.09±42.88	14.19±28.14
Colloid Group (n=12)	100.00	- 12.30±17.32	- 0.26±21.49	0.84±15.79
IVIG Group (n=12)	100.00	- 5.39±27.98	1.51±14.04	- 8.52±15.05
Untreated Sepsis Group (n=12)	100.00	- 25.24±17.97*	- 9.6±30.17	- 18.97±19.83*

All values are mean ± SD for each group. (*p<0.05).

of ring electrodes. Data were collected and evaluated by means of a Biopac MP 30 acquisition system and Student Lab Pro version 3.6.7 software (BIOPAC Systems, Inc., Santa Barbara, USA). During the CNAP recordings, rectal temperatures of the rats were monitored by a rectal probe (HP Viridia 24-C, USA) and the temperature of each rat was kept around 36-37°C by a heating pad.

Nerve Conduction Velocity (NCV) Measurements

Antidromic NCV was assessed in the tail nerve. The bipolar stimulating electrode was placed at the tail proximally. The recording ring electrodes were placed 5 cm and 10 cm with respect to the stimulating electrodes.[17] NCV was calculated by the distance between the two recording electrodes measured using a Vernier caliper divided by the difference of distal subtracted from proximal latency.

Statistical Analysis

The results are presented as mean ± SEM and the statistical analysis of data was performed by software SPSS using analysis of variance (ANOVA). $p<0.05$ was accepted as statistically significant. When an overall difference was obtained, group differences were assessed by post hoc analysis. Factors were sessions (preoperative and 6th hour, 12th hour, 24th hour after surgery) and treatment (sham-operated group, sepsis group, sepsis + IV colloid-treated group, sepsis + IV Ig-M-enriched IVIG-treated group). Dependent variables were motor NCV (MNCV) and amplitude.

RESULTS

There were no statistically significant differences between groups with respect to weights of the rats and the initial NCV levels. NCV levels did not statistically decrease in the sham, colloid-treated, and IVIG-treated groups (Table 1). On the contrary, NCV levels were decreased statistically ($F(3.30)=5.4$; $p=0.004$) and did not return to normal levels at the 6th hour ($p=0.017$) or even at the 24th hour ($p=0.030$) in the untreated sepsis group (Table 1, Fig. 1).

Decrease in NCV was maximum at the 6th hour and never returned to the initial level in the untreated sepsis group. The decline was 25.24% at the 6th hour and 18.97% at the 24th hour (Table 2).

DISCUSSION

There has been an increasing attention to CIP recently due to the high mortality and morbidity rates. In the late phase of sepsis, primary axonal degeneration in the motor and sensory fibers may result in CIP.

The seriousness of the underlying diseases, muscle relaxants and mechanic ventilation may delay the diagnosis of polyneuropathy. Generally, neurological examination can be misleading due to the protection by some means of tendon reflexes even in the serious polyneuropathies. Electrophysiological investigations seem to be necessary to overcome the difficulties mentioned before.[4,5,18,19] The amplitude reduction

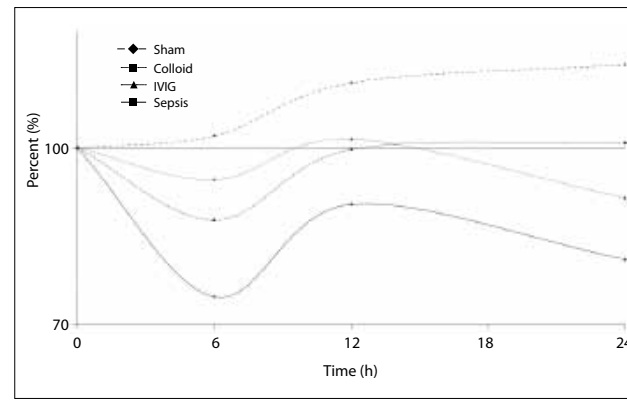

Fig. 1. Alterations of NCV (%).

has been accepted as the earliest prognostic electrophysiological finding.[2,3,5,6,20] Latency alterations may also accompany the CMAP and sensory nerve action potential (SNAP) amplitude decrease.[6] CMAP and SNAP amplitude decrease and latency alterations can be observed one or two weeks before the onset of clinical signs.[5] However, fibrillation potentials and sharp waves can not be observed before three weeks. If myopathy accompanies neuropathy, then CMAP duration also increases as an electrophysiological sign.[20,21] Although electrophysiological findings cannot be observed one or two weeks before the onset of clinical signs in ICU patients, our previous results have indicated that electrophysiological findings as an increase in latency and a decrease in CMAP amplitude appear in the first 24 hours after experimental sepsis.[6]

It was postulated that, in addition to the alterations of CMAP, SNAP and latency, measured NCV values may be normal in the early phases of sepsis, elongated in the late periods and normal in the recovery period.[4] On the other hand, there are also some reports indicating a slight elongation of NCV during the early phases.[2,4,5]

Druschky et al.[7] found a moderate decrease in NCV in addition to CMAP and SNAP amplitude decrease in CIP, which was not statistically significant. Mohr et al.[8] demonstrated CMAP and SNAP amplitude decrease in all of the sepsis patients with CIP and found moderate NCV decrease in only two patients.

In this study, there was a 25.24% statistically significant decrease in NCV in the group with no treatment at the 6th hour after sepsis induction, the decrease was persistent at the 24th hour, and the values did not reach the pre-op level (Table 1 and Table 2). Therefore, we think that the decrease in NCV may be an important electrophysiological sign in the early stage of sepsis and that awareness of the early electrophysiological signs is important for prophylaxis and immediate treatment for CIP.

Except for antibiotics, the common strategies applied in sepsis to reduce the high mortality are limited to some supportive treatments. One of these recent treatment strategies is modulating the inflammatory response in the early phase of CIP. If SIRS and sepsis are accepted as diseases of the immune system, as with the other autoimmune diseases, it is thought that instead of targeting only one mediator in the immunologic cascade, neutralization of various bacterial products and endotoxins by IVIG administration will be a more effective treatment strategy and will prevent polyneuropathy development in sepsis. IVIG can modulate the immunological cascade and the defense systems.[22-27] Therefore, IVIG administration just after SIRS development and in the early phase of sepsis possibly blocks the earliest induced cytokine tumor necrosis factor (TNF) in the inflammatory processes and the other inflammatory agents by neutralizing the bacterial endotoxins and will reduce the mortality rate and prevent CIP development in sepsis. Microcirculation deterioration and the permeability increase seen in sepsis facilitate the transportation of inflammatory mediators and potentially toxic substrates into the axons. Furthermore, cytokines (especially TNF-α), which are an important part of the immunological cascade with an important role in MOF production, have direct toxic effects on the peripheral nerves. TNF is one of the most important and the earliest-secreted cytokines and also has a key role in MOF and acute respiratory distress syndrome production and is thought to be the responsible for CIP development.[7,28-30] E-selectin increase in the epineural and perineural vessel endothelia seen in septic patients with CIP is also thought to be induced with cytokines like TNF-α and interleukin (IL)-1.[3,7,30] Transient rise in TNF especially in the first few hours of sepsis was shown by Xuan et al.[31] They showed in their experimental sepsis model that 60 minutes after the endotoxin injection, TNF-α increased, and this effect lasted for 120 min and returned to normal values at 240 min. The administration of human derived IG (IVIG) before the endotoxin injection prevented the TNF increase. Since it is almost impossible to block or prevent the development of the cytokine-induced immunological cascade in the majority of the clinical cases by IVIG treatment, IVIG administration may be more beneficial for the ICU patients vulnerable to sepsis in a prophylactic manner.[31] Polyclonal IVIG antibodies, which are especially produced for endotoxins and gram-negative bacteria, have a neutralizing effect on Q-antigen and endotoxins.[32,33]

It is postulated that cytokines such as TNF-α and IL-6 may be involved in the pathophysiology of CIPNM. In a retrospective chart analysis of sepsis patients with MOF in which decreased CMAP amplitudes with a slight decrease in sensory NCV were observed, no CIP was observed in the early IVIG-administered patients.[8] In our study, no NCV alteration was observed in the IVIG-treated group (IVIG administered after CLP and before sepsis development), suggesting that early IgM-enriched IVIG treatment might have preventive effects on polyneuropathies in sepsis.

According to Schedel,[32] endotoxins might have directly toxic effects on peripheral nerves, and inhibition of the biological effects of endotoxins might be an important strategy to prevent CIP development.

The results of our study support this hypothesis, since the NCV levels were unchanged in the IVIG-treated group while the NCV levels decreased in the untreated sepsis group.

In the colloid-treated group, NCV levels were also unaltered. Thus, since no decrease in NCV was observed in the group with early volume replacement with colloid, it is hard to suggest that application of the IVIG will be beneficial in the early phase.

On the other hand, our observation that NCV levels never altered in the colloid-treated group in which the effective intravascular volume was conserved is important and should be taken into consideration (Table 1, Fig. 1). As it is known, sepsis is also related with relative or absolute hypovolemic state besides the triggered immunologic cascades. Relative hypovolemia in sepsis can lead to reduced circulating blood volume and hypotension. The volume deficit occurs in the absence of obvious fluid loss and is due to vasodilatation and to alterations in the endothelial barrier. Altered baroreflexes cause vasodilation and hypotension. Cardiac output drops by hypotension and hypovolemia. Microcirculation and end-organ oxygenations deteriorate and MOF occurs. It is known that the central nervous system is the most sensitive tissue to hypoxia and the first affected system in sepsis. Therefore, we think that effective fluid resuscitation and adequate intravascular volume are important in the early stage of sepsis and related multiple organ dysfunctions. We believe that early and adequate intravascular volume replacement may be an important factor in the early stage of sepsis preventing neuromuscular abnormalities. Our results in the colloid-treated group support this opinion.

In conclusion, NCV is decreased in the early stage of experimental sepsis and it may be accepted as an early electrophysiological sign in CIP. Either IgM-enriched IVIG or adequate fluid replacement appears to prevent the decrease in the NCV in the early phase of experimental sepsis.

We were not able to clarify the underlying mechanisms to explain why both the IgM-enriched IVIG and colloid replacement prevented the decrease in NCV in the early phase of experimental sepsis. Results were statistically indistinguishable between the IVIG- and colloid-treated groups. The lack of statistical differences between these groups is noteworthy, and there is a need to clarify the mechanisms of action with further randomized, clinical and experimental trials.

Key Message

NCV is decreased in the first 24-hour period of experimental sepsis and it may be accepted as an early electrophysiologic sign in CIP.

Early intravascular volume replacement and increase in oncotic pressure are important in the first 24-hour period of experimental sepsis. It may be preventative for neuromuscular deterioration in sepsis.

Early IVIG treatment may be preventive for the decrease in NCV in the first 24-hour period of experimental sepsis.

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