Journal of Neurological Sciences [Turkish] **31:(1)**# 39; 115-125, 2014
http://www.jns.dergisi.org/text.php3?id=747
Research Article

Ischemia Modified Albumin Levels in Spinal Cord Ischemia/Reperfusion Injury: an Experimental Study

Hayri KERTMEN[1], Bora GÜRER[1], Altuğ HASANBASOĞLU[2], Ahmet MENTEŞE[3], Erdal Reşit YILMAZ[1], Özlem UZUN[4], Diler Us ALTAY[3], Ata Türker ARIKÖK[5], Zeki ŞEKERCİ[1], Süleyman TÜREDİ[6]

[1]Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Neurosurgey Clinic, Ankara, Turkey [2]Turkish Union of Chambers and Commodity Exchanges University of Economics and Technology Hospital, Emergency Medicine Department, Ankara, Turkey [3]Karadeniz Technical University, Faculty of Medicine, Department of Biochemistry, Trabzon, Turkey [4]Ministry of Health İstanbul Bağcılar Education and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey [5]Ministry of Health, Diskapi Yildirim Beyazit Education and Research Hospital, Department of Pathology, Ankara / Turkey [6]Karadeniz Technical University, Faculty of Medicine, Department of Emergency Medicine, Trabzon, Turkey

Summary

Background: Spinal cord ischemia/reperfusion (I/R) injury involves evident ischemia-mediated oxidative stress. Ischemia-modified albumin (IMA) has emerged as a novel and sensitive ischemia and oxidative stress biomarker, although it has not been previously investigated in ischemic spinal cord injury (SCI). This study was therefore intended to investigate serum IMA levels in a rabbit model of experimentally induced ischemic SCI.
Method: Spinal cord ischemia was induced in 53 mature, male New Zealand rabbits weighing 2.5-3 kg using the aortic occlusion model. Animals were divided into 10 groups (sham, ischemia and different duration I/R groups and their respective controls). IMA, tissue and blood malondialdehyde (MDA), tissue and blood myeloperoxidase (MPO) activity levels and histopathological damage scores were then compared.
Results: Ischemia-modified albumin levels rose rapidly when ischemia was induced to the spinal cord. They then declined to levels similar to those of the control groups when reperfusion was established. Serum IMA levels exhibited a tendency to rise over time in both the control and I/R groups compared to the sham group. We observed no correlation between IMA levels and blood and tissue MDA and MPO levels ($p>0.05$ for all correlations). We determined only a low correlation between histopathological score and serum IMA and MDA levels.
Conclusions: The results from this pioneering study identified a high level of IMA in spinal cord I/R injury, indicating that IMA is a potentially valuable diagnostic or predictive technique for ischemic SCI and its complications.

Key words: Ischemia-modified albumin, ischemia-reperfusion injury, rabbit, spinal cord

Spinal Kord İskemi/Reperfüzyon Hasarında İskemi Modifiye Albumin düzeyleri: Deneysel Çalışma

Özet

Giriş: Spinal kord iskemi/reperfüzyon hasarında iskemi nedenli oksidatif stres önemli yer teşkil eder. Ischemia-modifiye albumin (IMA), yeni kullanıma giren, iskemi ve oksidatif

stresin duyarlı bir biyomarkırı olup, daha önce iskemik spinal kord hasarında çalışılmamıştır. Bu çalışmada deneysel spinal kord iskemi hasarında IMA düzeylerindeki değişikler incelendi.
Metod: Elliüç adet yetişkin, erkek, 2,5-3 kg ağırlıklarında, Yeni Zelanda tavşanına aort oklüzyon metodu kullanılarak spinal kord iskemisi oluşturuldu. Denekler 10 gruba (sham, iskemi ve değişik zaman aralıklarında iskemi/reperfüzyon yapılan gruplar ve kontrolleri) ayrıldı.
IMA, doku ve kan malondialdehyde (MDA) ve myeloperoxidase (MPO) aktivite düzeyleriyle histopatolojik hasar skorları karşılaştırıldı.
Bulgular: IMA düzeylerinin iskemiyi takiben hızlı bir şekilde arttığı gözlemlendi. Reperfüzyonu takiben ise kontrol gruplarıyla aynı düzeye düştüğü izlendi. Serum IMA düzeylerinin zamanla yükseldiği kontrol ve I/R grupları karşılaştırıldığında görüldü. Ancak IMA düzeyleriyle kan ve doku MDA ve MPO düzeyleri arasında korelasyon tespit edilmedi (tüm kıyaslamalar için $p>0,05$). Histopatolojik skorlar ile serum IMA ve MDA düzeyleri arasında düşük korelasyon görüldü. Sonuçlar: Bu çalışmanın sonuçlarında spinal kord iskemi/reperfüzyon hasarında yüksek IMA düzeyleri tespit edildi. Yüksek IMA düzeylerinin spinal kord iskemisinin ve komplikasyonun bir göstergesi olabileceği sonucuna varıldı.

Anahtar Kelimeler: İskemi-modifiye albumin, iskemi-reperfüzyon hasarı, spinal kord, tavşan

INTRODUCTION

Surgery to the thoracoabdominal aorta and spine may cause spinal cord ischemia/reperfusion (I/R) injury leading to paraplegia[4,6]. The pathophysiological mechanisms underlying hypoxic/ischemic injury to the spinal cord are still unclear. However, the mechanism of acute spinal cord dysfunction is believed to result from ischemic damage arising during cross-clamping. Ischemia may arise in the event of permanent exclusion of the essential arterial blood supply to the spinal cord, or if the spinal cord blood flow is temporarily interrupted[18]. Neurological damage arising at time of insult is known as "primary injury". Activation of endogenous substances increases secondary damage in spinal cord injury. Inflammation and free radical formation are significant components of the pathological mechanisms involved in secondary damage[9].

The metal binding capacity of albumin to transition metals such as copper, nickel and cobalt declines under acute ischemic conditions. The result is a metabolic variant of the protein generally known as ischemia modified albumin (IMA)[22]. Alterations to the binding capacity of albumin for cobalt may take place during I/R due to acidosis, reduced oxygen tension and free radical generation[23]. Ischemia modified albumin is a novel and sensitive biomarker of such acute ischemic conditions as myocardial ischemia, skeletal ischemia, mesenteric ischemia, stroke and pulmonary embolism[11-14]. It has also been proposed as a useful predictor of prognosis of cardiac arrest[21]. Ischemia modified albumin has also recently been licensed by the United States Food and Drug Administration for diagnostic use in suspected myocardial ischemia[20].

Although swift diagnosis and preventive interventions are crucial if spinal cord function continuity is to be preserved, there is no satisfactorily sensitive standard method for diagnosing or predicting spinal cord injury (SCI) and complications thereof. A sensitive biochemical marker is therefore needed to serve as an adjunct to diagnosis and increase SCI management efficiency.

Spinal cord injury involves clear ischemia-mediated oxidative stress; IMA has emerged as a novel and sensitive ischemia

and oxidative stress marker, although it has not been previously investigated in SCI. This study was therefore intended to investigate serum IMA levels in a rabbit model of experimentally induced SCI.

MATERIAL AND METHODS

Study Design

This was a randomized, controlled, non-blinded interventional animal study, the protocol for which was approved by the Turkish Ministry of Health Ankara Hıfzıssıhha Institute Experimental Animals Ethical Committee.

Setting and Selection of Subjects

Fifty-three mature, male New Zealand rabbits weighing 2.5-3 kg received spinal cord ischemic injury using the aortic occlusion model. The animals were kept in steel cages until the day of the experiment at a room temperature of 22 0C, and were given water and standard rabbit chow. For the final 12 h before the experiment they were given only water.

Intervention

The rabbits were then divided into 10 groups;

Group I (n=4) – sham group (blood and tissue specimens taken 20 min after laparotomy alone with no ischemia or reperfusion)

Group II (n=6) – ischemia group (blood and tissue specimens taken 20 min after spinal cord ischemia alone with no reperfusion)

Group III (n=4) – 1-h control group (blood and tissue specimens taken 80 min after laparotomy alone without ischemia or reperfusion)

Group IV (n=6) – 1-h I/R group (blood and tissue specimens taken after 1-h reperfusion after 20-min spinal cord ischemia)

Group V (n=4) – 3-h control group (blood and tissue specimens taken 200 min after laparotomy alone with no ischemia or reperfusion)

Group VI (n=6) – 3-h I/R group (blood and tissue specimens taken after 3-h reperfusion following 20-min spinal cord ischemia)

Group VII (n=4) – 6-h control group (blood and tissue specimens taken 380 min after laparotomy alone with no ischemia or reperfusion)

Group VIII (n=7) – 6-h I/R group (blood and tissue specimens taken after 6-h reperfusion following 20-min spinal cord ischemia)

Group IX (n=4) – 24-h control group (blood and tissue specimens taken 1460 min after laparotomy alone with no ischemia or reperfusion)

Group X (n=8) – 24-h I/R group (blood and tissue specimens taken after 24-h reperfusion after 20-min spinal cord ischemia)

The study was performed on 53 rabbits; experimental groups were randomized into control groups of four rabbits each, while the ischemia groups consisted of 6-8 animals each (bearing in mind the probable loss of experimental subjects). During allocation into randomized groups, the 53 rabbits of the same weight were numbered from 1 to 53. Rabbits were randomly allocated into groups one by one. To maintain uniformity through the study, interventions were conducted concomitantly on each rabbit in each group. Intramuscular injection of 10 mg/kg of xylazine and 50 mg/kg ketamine was used for general anesthesia. Spontaneous respiration was observed without the need for respiratory support throughout anesthesia. Experimental animals' body temperatures were maintained at 37oC throughout surgery and until the end of anesthetic effect by means of heating pads.

In order to establish I/R injury in the spinal cord, the abdomen was entered with an average 7-8 cm median laparotomy

incision under sterile conditions, the intestine was mobilized to the right and the abdominal aorta explored. Approximately 1 cm below the renal artery, the aorta was clamped using an aneurysm clip of 70 g closing force (Yasargil, FE721, Aesculap, Germany) under a surgical microscope. The aorta was kept clipped for 20 min. In the groups to be administered reperfusion as well as ischemia (groups IV, VI, VIII and XI), the clips were removed after 20-min ischemia and reperfusion established. Blood flow to the distal of the clip site was visualized. Only a similar laparotomy incision was performed in the control groups.

All blood samples were obtained from the same place from the abdominal aorta. Animals were sacrificed by injection of pentobarbital (200 mg/kg), and spinal cord specimens were collected by carefully performed laminectomy between L1 and S1. Also, tissue samples from ileum and muscle from lower extremity were collected. Tissue samples from the spinal cord were stored frozen until analysis.

Laboratory Analysis

Ischemia modified albumin levels were measured. Myeloperoxidase (MPO) and malondialdehyde (MDA) levels were also measured concomitantly for comparison with IMA values by a biochemist blinded to which groups the animals came from.

Ischemia modified albumin measurement

Serum and plasma samples were prepared with 15 min of centrifugation at 1800 g. The specimens were pipetted into Eppendorf tubes and stored at –80 °C.

Reduced cobalt to albumin binding capacity (IMA level) was analyzed using the rapid and colorimetric method of Bar-Or et al[2]. The results were reported as absorbance units (ABSUs).

Blood and tissue MPO measurement

Serum MPO activity was assessed by measuring the H2O2 dependent oxidation of o-dianosidine[3]. Briefly, 15 uL serum was incubated with 290 µL of 50 mmol/L potassium phosphate buffer, pH 6.0, containing 0.167 mg/mL o-dianisidine dihydrochloride and 0.0005% hydrogen peroxide. Product formation was linear for 5 minutes and measured at 460 nm at 25oC (ε = 11300 $M^{-1}.cm^{-1}$). Results were expressed as units of MPO/L, whereby 1 unit of MPO was defined as the amount of enzyme degrading 1 µmol H_2O_2 per min at 25°C.

Tissue samples were thawed on ice. 0.025 g of rabbit spinal cord tissue was homogenized (Ika T-18 Basic Ultra Turrax Homogenizer, USA) in 1 mL of ice-cold 50 mM potassium phosphate buffer, pH 6.0, for 5 min at 13500 rpm on ice. Homogenate was centrifuged at 16,000 rpm for 30 min at 4°C. The pellet was resuspended in the same buffer with 0.5% hexadecyltrimethylammonium bromide (HETAB) and 10 mM EDTA. The samples were frozen and thawed three times before another centrifugation (16,000 rpm at 4°C). MPO activity in the supernatant was assayed as described by Bradley et al, with a little modification[3]. Briefly, 20 uL of supernatant was mixed with 290 µL of 50 mmol/L potassium phosphate buffer, pH 6.0, containing 0.167 mg/mL o-dianisidine dihydrochloride and 0.0005% hydrogen peroxide. Product formation was linear for 5 minutes and measured at 460 nm at 25°C (ε = 11300 M-1.cm-1). Results were expressed as units of MPO/mg protein (or Units of MPO/g wet tissue).

Blood MDA measurement

Malondialdehyde levels in plasma samples were established using the Thiobarbituric Acid Reactive Substance (TBARS) method developed by Yagi in 1994[25].

Tissue MDA measurement

A piece of testis tissue was used to measure MDA levels. The sample was minced and homogenized in an ice-cold 1.15% KCl solution containing 0.05% Triton X-100 using an Ultra-Turrax T25 homogenizer. Tissue MDA levels were

determined using the method described by Mihara and Uchiyama[19]. Tetramethoxypropane was used as a standard, and MDA levels were calculated as nmol/g of wet tissue.

Histological analysis and staining

In order to determine ischemia-related changes, 1-cm spinal cord segments, ileum and muscle tissues were collected for histopathological examination. Specimens were kept in 10% neutral formalin solution for 72 h. Following routine histopathological procedures, prepared paraffin blocks were cut into 5-µ thick sections. After than species had been stained with hematoxylin-eosin, they were examined under microscopy for hemorrhage, congestion, edema, inflammation and neuronal degeneration by a pathologist blinded to the study groups. Tissues were scored 0= None, 1= Minimal, 2= Mild, 3=Average or 4= Severe for each parameter[26].

Statistical analysis

Analysis of the IMA, MPO and MDA levels of the same-time control and ischemia or I/R groups was performed using the Mann Whitney U-test. Time dependent changes in parameters were analyzed using Kruskal Wallis analysis of variance (Mann Whitney U-test with corrected Bonferroni test). Spearman's correlation analysis was used to assess the relationship between biochemical parameters and histopathological scores. Statistical significance was set at $p<0.05$.

RESULTS

Biochemical parameters

Chronological changes in biochemical parameters among the groups are given in Table-1.

From our results, IMA levels rose rapidly when spinal cord ischemia was established and then fell to levels similar to those of the control groups when reperfusion was applied. An increasing trend in serum IMA levels was seen in the control and I/R groups compared to the sham group. However, the difference between the groups representing the same time periods was not significant. This time-dependent change in IMA levels is shown in Figure-1.

Although the desired level of significance ($p<0.001$) was not obtained when Bonferroni correction was applied in the comparison of any of the parameters we analyzed, p values for comparisons regarding IMA alone are shown in Table-1. We ascribed this to the large number of groups involved, and also to the number of experimental animals in each group being limited as a requirement of ethical principles.

No correlation was determined between IMA levels and blood and tissue MDA and MPO levels ($p>0.05$ for all correlations).

Histopathological examination

No findings of SCI were determined at histopathological examinations performed in the sham group and control groups for all time periods (groups I, III, V, VII and IX) in terms of hemorrhage, congestion, edema and neuronal degeneration. However, evident histopathological injury was seen in the I/R injury groups (groups II, IV, VI, VIII and X) (Table 2, Figure 2). The results emerging from analysis of correlation between histopathological scores and biochemical parameters are shown in Table-3. There was a low correlation between histopathological score and serum IMA and MDA levels only.

None of the ileum and muscle tissues showed any evidence of ischemia.

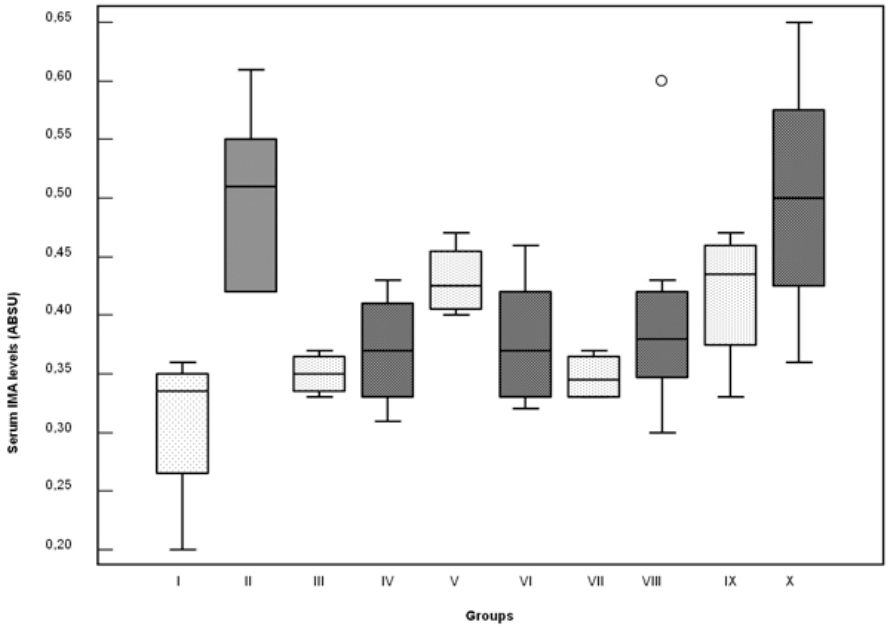

Figure 1: *Time-dependent serum IMA levels in the groups.*

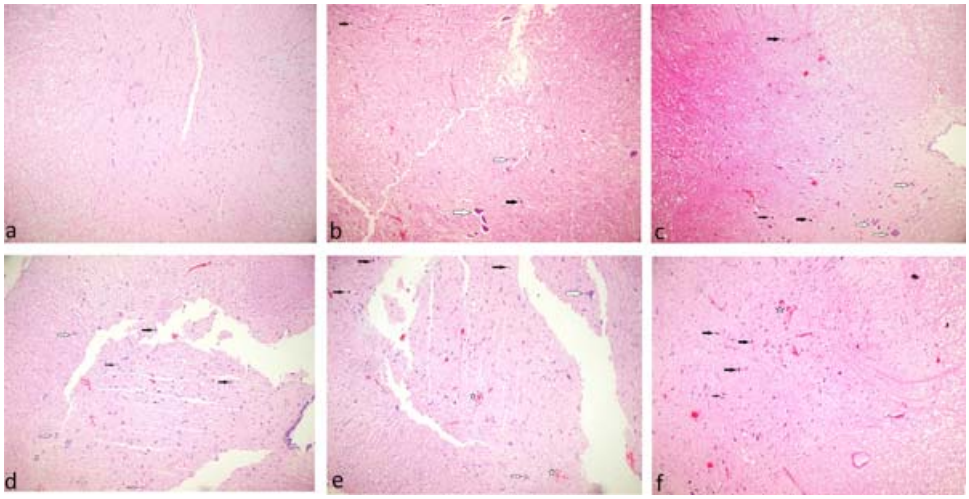

Figure 2: *Histopathological appearance of evident I/R injury in the ischemia and I/R groups compared to the control groups.*

a: Sham group, showing regular spinal cord parenchyma (H&E X10).

b: Group II, showing degenerated neurons (filled arrows) in the edematous surface. Intact neurons are shown with hollow arrows (H&E X10).

c: Group IV, showing degenerated neurons (filled arrows) in the edematous surface. Intact neurons are shown with hollow arrows (H&E X10).

d: Group VI, showing more degenerated neurons (filled arrows) in the more edematous surface. Intact neurons are shown with hollow arrows (H&E X10).

e: Group VIII, showing more edema and degenerated neurons (filled arrows); note the only few normal appearing neurons (hollow arrows). Hemorrhagic focus is shown by stars. (H&E X10).

f: Group X, showing the most severe edema and degenerated neurons (filled arrows); note the only few normal appearing neurons (hollow arrows). Hemorrhagic focus is shown by stars (H&E X10).

Table 1: Time-dependent changes in ischemia modified albumin, MDA, and MPO levels in SC I/R injury.

Parameters	Groups									
	Group I-Sham group	Group II-Ischemia group	Group III-1-h control	Group IV-1-h I/R group	Group V-3-h control	Group VI-3-h I/R group	Group VII-6-h control	Group VIII-6-h I/R group	Group IX-24-h control	Group X-24-h I/R group
IMA(ABSU)										
Median	0.335[a,b,c]	0.510[a,d,e,f,g,h]	0.350[d,i]	0.370[e,j]	0.352[b]	0.370[f,k]	0.345[g,l]	0.380[h,m]	0.435	0.500[c,i,j,k,l,m]
Percentiles 25-75	0.232-0.355	0.420-0.565	0.332-0.367	0.325-0.415	0.327-0.375	0.327-0.430	0.330-0.367	0.340-0.430	0.352-0.465	0.412-0.602
MDA(nmol/ml)										
Median	0.062	0.041	0.073	0.225	0.115	0.115	0.145	0.136	0.162	0.147
Percentiles 25-75	0.045-0.078	0.038-0.091	0.061-0.093	0.064-0.67	0.106-0.730	0.093-0.138	0.117-0.17	0.12-0.197	0.113-0.176	0.137-0.201
MPO (ng/ml)										
Median	58.8	34.3	41.5	60.5	29.9	56.5	45.6	67.0	24.3	35.1
Percentiles 25-75	29.6-73.5	23.7-42.3	27.1-47.1	38.5-82.9	21.7-40.3	50.9-87.3	17.7-79.5	34.6-92.1	23.6-44.8	18.1-39.6
Tissue MDA (nmol/g)										
Median	165.5	249.0	246.0	150.0	155.5	249.5	223.5	192.0	238.5	278.5
Percentiles 25-75	139.5-175.5	225.5-278.3	212.0-313.7	131.7-192.5	109.0-193.7	174.0-307.5	148.5-261.7	140.0-202.0	202.0-288.5	153.7-347.3
Tissue MPO (ng/g)										
Median	30.1	12.8	63.7	34.2	7.2	21.5	15.6	29.4	12.9	25.9
Percentiles 25-75	9.5-214.9	6.8-66.8	21.9-117.2	23.9-46.1	2.65-11.7	14.1-125.5	13.1-626.3	10.7-136.8	5.5-87.7	14.1-36.8

Note: ABSU=Absorbance unit

a,d,e,f,g,i,j,l p=.01; b,k p=.02; c, p=.008; h,m p=.04 for serum IMA

Table 2: Comparison of groups' histopathological damage scores

Parameters	Groups									
	Group I-Sham group	Group II-Ischemia group	Group III-1-h control	Group IV-1-h I/R group	Group V-3-h control	Group VI-3-h I/R group	Group VII-6-h control	Group VIII-6-h I/R group	Grup IX-24-h control	Grup X-24-h I/R group
Hemorrhage	0	1±0.6	0	1.5±0.5	0	1.8±0.7	0	2±0.5	0	2.5±0.5
Congestion	0	1±0.6	0	2.1±0.7	0	2±0.9	0	2.1±0.7	0	2.6±0.5
Edema	0	1±0.6	0	1.6±0.5	0	2.1±0.7	0	2±0.5	0	2.6±0.5
Neuronal degeneration	0	1.6±0.5	0	2±0.6	0	2.8±0.7	0	3.2±0.7	0	3.5±0.5
Total score	0	$4.6\pm1.9^{a,b,c,d}$	0	$7.5\pm1.5^{a,e,f}$	0	$8.8\pm2.3^{b,g}$	0	$9.4\pm0.9^{c,e,h}$	0	$11.2\pm1.3^{d,f,g,h}$

Note: Values are expressed as mean ± SD

a,d,e p=.02; b, p=.009; c,f p=.003; g, p=.03; h, p=.018

Table 3: Correlation of histopathological damage and biochemical parameters in the study groups

	Histopathological damage score	
	R	p
Serum IMA&	**0.276**	**.046**
Serum MDA&	**0.286**	**.038**
Serum MPO&	0.161	.248
Tissue MDA&	0.141	.313
Tissue MPO&	0.121	.389

DISCUSSION

The spinal cord is sensitive to ischemia. Spinal cord I/R injury leading to delayed paraplegia is a well-known and very serious complication following surgery to the thoracoabdominal aorta[8,10,27]. Oxygen free radicals play a major role in membrane lipid, essential protein and DNA destruction post-injury. However, the exact biomechanism by which I/R injury occur in the spinal cord is not fully established. Necrosis is regarded as the main mechanism of apoptosis after SCI. This is followed by a progressive injury process (secondary injury) that initiates apoptosis[7]. Although a number of studies have shown that the risk of postoperative paraplegia declined with the application of new techniques, preventing spinal cord ischemic injury represents a major concern in aortic surgery[24]. The reported incidence rate of paraplegia ranges between 2.9% and 23%. Complications are still difficult to predict and prevent, despite improved surgical techniques, including systemic deep hypothermia, distal aortic perfusion, cerebrospinal fluid drainage, intercostal artery implantation, use of motor sensory or somatosensory-evoked potentials and pharmacological interventions[1].

Despite the fact that rapid diagnosis and preventive interventions are critical for preserving continuity of functions of the spinal cord, there is no satisfactorily sensitive standard diagnostic or predictive method for SCI and its complications. A sensitive biochemical marker would thus be of importance as it would serve as an adjunct to diagnosis and increase efficiency of SCI management.

Ischemia modified albumin is a new and sensitive biomarker of ischemia and oxidative stress. Ischemia modified albumin levels may rise during ischemia reperfusion and may affect any organ[17]. According to available databases, this study is the first to examine IMA as a biochemical parameter of SCI. According to our results, IMA levels rise rapidly with spinal cord ischemia and quickly decline to levels similar to those of the control groups after reperfusion. Serum IMA levels were higher in the experimental animals exposed to 20 min only of ischemia (Group II) compared to the sham group and other control groups exposed to no ischemia. From that perspective, IMA levels may be interpreted as a biochemical parameter that rises in the early period in the diagnosis of ischemia-related SCI.

According to the findings we obtained from experimental subjects exposed to I/R for different periods, histopathological injury increases time-dependently. Although at first sight this might appear to be related to exposure to similar ischemia periods but longer administration of reperfusion, it may not be possible to ascribe the increase in injury to the application of a longer period of reperfusion alone. Groups administered longer reperfusions were exposed to longer periods of I/R injury. In addition, hemodynamic changes such as hypotension from exposure to anesthetics in particular might have led to increased damage. No such hemodynamic investigation was performed in this study due to the nature of our experimental protocol.

The highest IMA levels were determined in the ischemia groups. IMA levels declined following administration of reperfusion, but as well as a rise in histopathological damage as length of reperfusion increased, we also observed an increase in IMA levels. Although our results revealed a very low positive correlation between IMA levels and histopathological injury, we were unable to reach a definitive conclusion on the subject.

Compared with other tissues, the central nervous system possesses high levels of polyunsaturated lipids and metabolic rate with low antioxidant enzyme activity. In SCI models, oxidative stress initiates lipid peroxidation cascades. These then damage

the highly vulnerable cell membranes during the first few days after injury[5,16]. Malondialdehyde is a marker used for determining oxidative damage. Created by the reaction between polyunsaturated lipids and free radicals, MDA is an end product of lipid peroxidation[15]. In studies of I/R-related SCI, a decline in MDA levels is regarded as a finding of a reduction of injury[15]. Our results showed high MDA levels in experimental subjects exposed to I/R injury, and there was a similar very low correlation between histopathological injury and MDA levels. However, we cannot speak of a significant correlation between these two biochemical parameters that might be regarded as a marker of I/R injury.

A number of limitations apply to this study. Ischemia modified albumin is a new biomarker whose levels are significantly affected by a range of physiological variables including exercise and hydration. We were unable to control all those variables that might potentially affect IMA levels. Second, we did not compare all other biochemical markers and IMA in SCI. Another limitation is that we only investigated IMA levels for the first 24 h.

In conclusion, despite some limitations, the results from this pioneering study revealed a high level of IMA in spinal cord I/R injury, indicating that IMA is of potential diagnostic or predictive value for SCI and its complications and that it may be a valuable biochemical parameter in the investigation of spinal cord I/R injury.

Correspondence to:
Bora Gürer
E-mail: boragurer@gmail.com

Received by:
Revised by:
Accepted:

The Online Journal of Neurological Sciences (Turkish) 1984-2014
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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