EXPERIMENTAL STUDY

Evaluation of renal function in rats with moderate and mild brain trauma

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ABSTRACT

BACKGROUND: We aimed to diagnose possible acute kidney injury (AKI) with new early biochemical markers in patients who were admitted to the emergency department frequently with mild and moderate brain trauma, and to prevent possible complications, shorten the duration of treatment and hospital stay. With this purpose, we decided to reach our scientific target using the experimental rat model.

METHODS: Wistar albino rats were included our experiment. Fifteen rats were randomly separated into three groups: Sham control (n=1: Underwent craniotomy alone), control (n=7: Without craniotomy), and trauma group (n=7: Underwent craniotomy followed by brain injury).

RESULTS: There were no significant differences groups creatinine levels within 0 and 24 h (0.35±0.02 and 0.33±0.03, respectively, $p>0.05$). Plasma NGAL and KIM1 concentrations were statistically significant different in both control and trauma groups (Friedman $p<0.05$) and significant differences at both NGAL and KIM-1 concentrations at dual comparisons by means of all sampling time (0–2 h, 0–24 h, and 2–24 h) (Wilcoxon $p<0.001$, after Bonferroni correction).

CONCLUSION: The presence of AKI in patients with mild-to-moderate brain trauma increases the risk of mortality. Early diagnosis of AKI reduces the hospitalization period and requiring of dialysis. Diagnosis of AKI within 24 h with early biomarkers and starting therapy is crucial issues.

Keywords: Acute kidney injury; neutrophil gelatinase-associated lipocalin; kidney injury molecule-1.

INTRODUCTION

Traumatic brain injuries (TBIs) have increased in recent years both in our country and in the world.[1] The majority of patients admitted to our hospital have fallen from height (generally from trees or walls) and traffic accidents. Although these conditions may result in acute kidney injury (AKI) depending on the severity of the trauma, we do not have enough studies showing the relationship between AKI and brain trauma. Only a few studies have investigated and reported a low incidence of AKI during brain trauma.[2–4]

The causes of the AKI are pre-renal causes and renal ischemia, which represent 60–70%. Therefore, in cases of severe hypovolemia, they are potential risks for AKI.[5,6] AKI is a sudden loss of kidney functions with the failure of urinary excretion, resulting in increased blood urea nitrogen (BUN) and high serum creatinine (sCrea) levels. Recently, AKI has been established according to new classification, the risk, injury, failure, loss of kidney function, and end-stage kidney disease was proposed to define and stratify the severity of AKI. These

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definitions used for diagnosis of AKI are only qualitative.[7–9] Fortunately, recent studies suggest that new biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) show promising results for quantitative definition of AKI.[10,11] The downstream proteomic analyses show that after experimental nephrotoxic and ischemic injury in plasma and urine, NGAL levels were significantly increased.[12–14]

Urinary KIM-1 is a type 1 transmembrane protein and is not normally detected in plasma or urine. Following tubular damage, within 2–6 h urine and plasma, KIM-1 levels are increased.[15,16] Serum cystatin C is a 13 kD endogenous protein derived from cysteine proteinase protein. All nucleated cells produce cystatin C and excrete almost all of it by glomerular filtration (GFR). Following decrease of GFR, serum cystatin C level starts to increase within 24 h and becomes remarkable after 48 h.[17–19]

NGAL is a protein that is released from renal injured epithelial in AKI. The NGAL concentration increases both in urine and plasma earlier than other renal function biomarkers such as sCrea and cystatin C.[11,12]

MATERIALS AND METHODS

Adult Wistar albino female rats, who have 250–300 g weight, were included in our experiment from the Animal Laboratory of Yeditepe University (Istanbul, Turkey). A total of 15 rats were randomly separated into three groups as follows: Sham control (n=1: Underwent craniotomy alone), control (n=7: Without craniotomy), and trauma group (n=7: Underwent craniotomy followed by brain injury).

In accordance with the environmental conditions like day and night, all the rats were observed by a veterinary in Yeditepe University Animal Laboratory within 24 h, providing them water and food requirements in metabolic cages. This study was approved by the Animal Care and Ethics Committee of Yeditepe University School of Medicine (date: 01.03.2016-decision no: 524).

Experimental Procedure of TBI

All the surgeries were done under sterile conditions. A special weight-drop device developed by Marklund et al.[20] and modified with lighter weight and shorter height by Kural et al.[21] was used to deliver a standard diffuse traumatic injury. After ensuring the anesthetic effect through intraperitoneal ketamine hydrochloride anesthesia (80 mg/kg) and xylazine (10 mg/kg), the rats were fixed in the prone position and 1 ml of blood was taken from the jugular vein into the potassium ethylenediaminetetraacetic acid (K2EDTA) tube. To prevent the loss of rats due to intracranial pressure caused by trauma, craniotomy (6×9 mm^2) was performed using a dental drill from the temporoparietal area (approximately 3 mm). Then, 5 g weight was allowed to fall freely from a height of 50 cm to induce only local TBI. For the sham group, we only performed craniotomy on one rat, and the brain was left uninjured. In the 2nd h after the trauma, 1 ml jugular blood was taken in the tube with K2EDTA from all rats. All the rats survived 24 h after brain injury.

All the physiological parameters such as activity, water, and forage consumption were monitored and found regular. After 24 h, the rats were anesthetized with an intraperitoneal injection of ketamine hydrochloride. After intracardiac blood drawing for biochemical markers, all rats were sacrificed, and the brain and kidneys were carefully taken out (intact) for histopathological examination into 10% formaldehyde. For the measurement of biochemical markers, all centrifuged plasma supernatants were kept 1 month at −80°C ultra-low temperature freezers till analysis. Both plasma NGAL and KIM1 concentrations were measured using the rat ELISA Kit (Catalog No: E0762Ra and E0549Ra, respectively) and cystatin C levels measured using the rat ELISA Kit (Catalog No: ab201281) according to manufacturer's instructions (Bioassay Technology Laboratory and Abcam). The assays are based on the method of quantitative sandwich enzyme immunoassay, and the intra-assay coefficients of variation were <8%, <6%, and 2.95%, respectively. Interassay coefficients of variation were 8–10% for NGAL and KIM-1 and 3.52% for cystatin C. Creatinine concentrations in plasma samples were measured with auto-analyzer (Roche Diagnostics) based on the Jaffe method.

Histopathological Examination

Axial sections were stained with hematoxylin and eosin and all the stained specimens were examined blindly under an Olympus BX40 light microscope by the pathologist. After histopathological examination, the rats with brain injury showed vascular dilatation and stasis (Fig. 1); in their kidney tissues, diffuse interstitial hemorrhage, vascular dilatation, and glomerular congestion were also found (Fig. 2). The semi-quantitative scores reflect the approximate percentage of brain injury and glomerular changes shown in the sections. Results were scored for brain and kidney, as Grade 0 (no changes), Grade 1 (dilatation), Grade 2 (dilatation and stasis), and Grade 3 (dilatation, stasis, and hemorrhage).

Statistical Analyses

Using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013), statistical analyses were performed. Results were explained as mean, standard deviation, minimum, and maximum. The Mann–Whitney U-test and the Kruskal–Wallis test were used for non-parametric statistical analyses. Differences between two dependent groups were determined by means of the Wilcoxon test; differences between more than 2 dependent groups were determined by means of the Friedman test. $P<0.05$ was considered statistically significant.

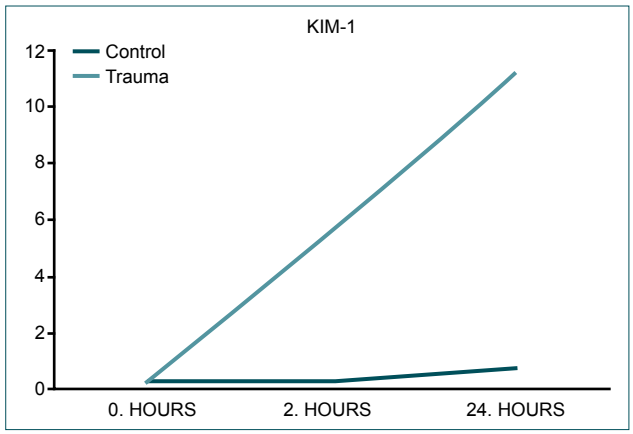


Figure 1. Plasma KIM-1 levels at the all time points in both groups.

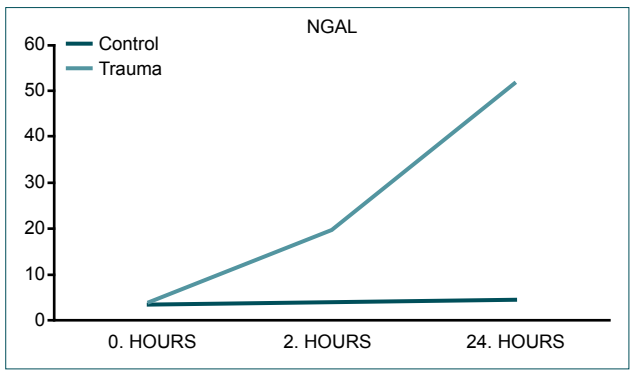


Figure 2. Plasma NGAL levels at the all time points in both groups.

ROC curves were constructed using both trauma and control subject plasma NGAL and KIM-1 levels in an attempt to form a specificity-sensitivity relationship; areas under the ROC curve were calculated according to standard methods. The diagnostic accuracy of the serum levels determined at study entry was expressed as the area under the receiver operating characteristic curve (AUC), which was derived from logistic regression analysis. These values were calculated for the cut-off from the AUCs.

RESULTS

Physiological Measurements

There was no difference between the physiological measurements of rats such as weight, respiration, heart rate, and rectal temperature before and after trauma.

Biochemical Analyses

Plasma creatinine (pCrea) and plasma cystatin C (pCys C) levels were measured at 0 hour (h) and then after sacrificing (24 h) for both groups. There were no significant differences in groups' pCrea (mg/dL) levels (0.35±0.02 and 0.33±0.03, respectively, p>0.05). Both groups' pCys C levels (pg/mL) were lower than detectable limit.

Comparisons of both plasma NGAL and KIM1 concentrations according to control and trauma groups are shown in Table 1. There were no significant differences by means of plasma NGAL and KIM1 levels at the beginning of this experiment in both groups. When we compared 0, 2, and 24 h, plasma NGAL and KIM1 concentrations were statistically significant different in both control and trauma groups (Friedman p<0.05). Plasma biochemical parameter levels in trauma group showed significant differences at both NGAL and KIM-1 concentrations at dual comparisons by means of all sampling time (0–2 h, 0–24 h, and 2–24 h) (Wilcoxon p<0.001, after Bonferroni correction). However, these differences were not observed in control group (Table 2).

Table 1. The comparison of serum KIM-1 and NGAL levels in both control and trauma groups within 0h, 2h and 24h

	Control	Trauma	p*
	Mean±SD Median (Min–Max)	Mean±SD Median (Min–Max)	
KIM1			
0h	0.31±0.09	0.28±0.08	0.456
	0.31 (0.2–0.4)	0.31 (0.2–0.4)	
2h	0.35±0.04	5.59±1	0.001
	0.35 (0.30–0.39)	6(3.29–6.33)	
24h	0.76±0.14	11.2±1.02	0.001
	0.75 (0.59–0.96)	10.9 (10.1–2.7)	
NGAL			
0h	3.72±0.5	3.69±0.5	
	3.79 (2.9–4.3)	3.94(2.9–4.3)	0.864
2h	4.29±0.6	19.51±4.22	
	4.2 3.57–5.09)	21.2 (11.0–22.6)	0.001
24h	4.54±0.16	51.1±1.7	
	4.54 (4.29–4.75)	51.6 (50.5–55.9)	0.001

*Mann-Whitney U test. P<0.05. KIM–1: Bioassay Technology Laboratory E0549Ra, Rat kidney Injury Molecule–1; NGAL: Bioassay TechnologyE0762Ra, Rat neutrophil gelatinase associated lipocalin; SD: Standard deviation; Min: Minimum; Max: Maximum.

When we compared control and trauma groups, statistically significant differences were found in these markers at both 2nd and 24th h of the experiment (p<0.001) (Figs. 3 and 4). We found significant variations of KIM-1 and NGAL levels between 0–2 h, 0–24 h, and 2–24 h in both control and trauma groups (Table 3). The significant correlations were found in both KIM-1 and NGAL levels within the trauma group (p<0.05).

To compare KIM-1 and NGAL levels for the prediction of AKI, we performed ROC curves. Both plasma markers had similar sensitivity and specificity for diagnosing. AKI (Table 4 and Fig. 5).

Table 2. Plasma KIM-1 and NGAL levels at dual comparisons using all sampling time (0h-2h, 0h-24h, 2h-24h)

	0.h	2.h	24.h	p*	p[1]	p[2]	p[3]
	Mean±SD Median(Min–Max)	Mean±SD Median (Min–Max)	Mean±SD Median (Min–Max)				
KIM1 (ng/mL)							
Control	0.31±0.09	0.35±0.04	0.76±0.14	0.009	0.400	0.028	0.028
	0.31 (0.2–0.4)	0.35 (0.3–0.39)	0.75 (0.59–0.96)				
Trauma	0.28±0.08	5.59±1	11.2±1.02	0.001	0.012	0.012	0.012
	0.31 (0.2–0.4)	6 (3.29–6.33)	10.9 (10.1–12.7)				
NGAL (ng/mL)							
Control	3.72±0.5	4.29±0.6	4.54±0.16	0.030	0.028	0.018	0.176
	3.79 (2.9–4.3)	4.2 (3.57–5.09)	4.54 (4.29–4.75)				
Trauma	3.69±0.5	19.51±4.22	51.1±1.7	0.001	0.012	0.012	0.012
	3.94 (2.9–4.3)	21.2 (11.0–22.6)	51.6 (50.5–55.9)				

*Friedman test p<0.05, [1]0h-2h, [2]0h-24h, [3]2h-24h. KIM-1: Bioassay Technology Laboratory E0549Ra, Rat kidney Injury Molecule-1; NGAL: Bioassay TechnologyE0762Ra, Rat neutrophil gelatinase associated lipocalin; SD: Standard deviation; Min: Minimum; Max: Maximum.

Histopathological Results

Brain and kidney pathological examination results were distinctly higher in the trauma group after 24 h as expected (Figs. 1 and 2). Light microscope images of minimal bleeding are shown in Figure 1. We found Grade 0–1 features in control group and S rats (respectively). In the trauma group, one of seven rats has Grade 1 and five of seven rats have Grade 2, and one of seven rats has Grade 1 features which were diagnosed by our pathologist.

DISCUSSION

The aim of this study is using an experimental animal model after TBI to show AKI in patients with new early biochemical markers. One of the obstacles to diagnose AKI is that increased creatinine and BUN cannot give a clear idea about whether renal failure is acute or chronic. According to Kidney Disease Improving Global Outcomes criteria, sCrea or pCrea and the measurement of urine output are used as primary diagnostic markers of AKI. Unfortunately, increased creati-

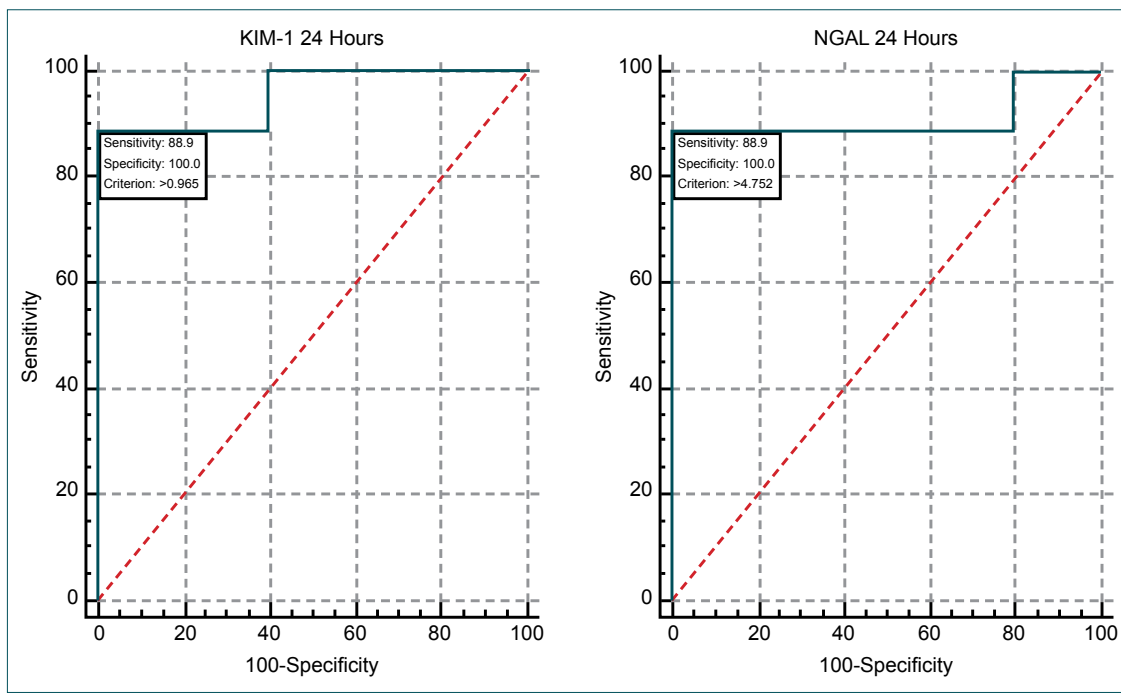


Figure 3. Evaluation of serum KIM-1 and NGAL for the diagnosis of AKI. Receiver operating characteristic curves (ROC) were drawn with the data of these markers from all rats.

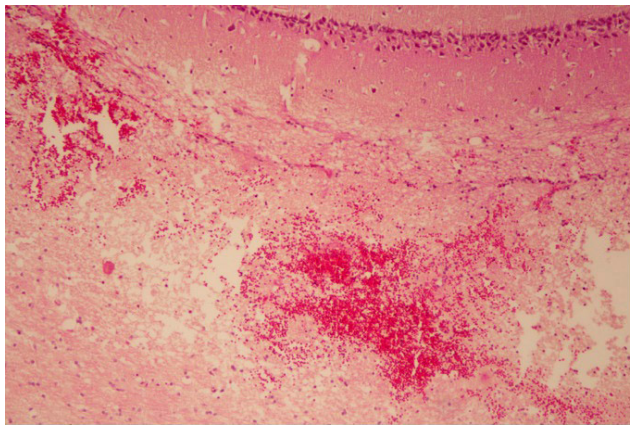


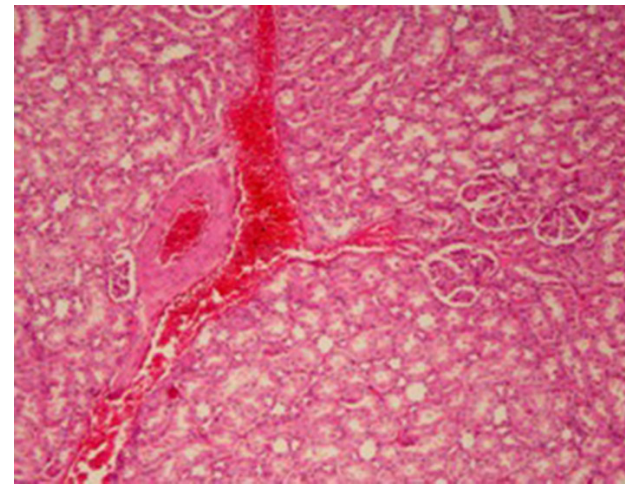
Figure 4. Plasma neutrophil gelatinase-associated lipocalin levels at the all-time points in both groups.

nine concentrations and other metabolites are observed with some time lag, that is, after damage of active nephrons that result in a decrease in GFR by approximately 50%.[17] One of the most important factors in the diagnosis of AKI is the detection of damage to the kidney before GFR decrease.[22,23]

Table 3. The comparison of biochemical parameters differences at time of sampling according to groups

	Control	Trauma	p*
	Mean±SD Median (Min–Max)	Mean±SD Median (Min–Max)	
KIM1			
0–2h	-0.04±0.1	-5.29±1.04	0.001
	-0.06 (-0.19–0.11)	-5.78 (-5.9–-2.9)	
0–24h	-0.44±0.22	-10.9±1.08	0.001
	-0.49 (-0.68–-0.19)	-10.7 (-12.4–-9.7)	
2–24h	-0.4±0.1	-5.6±1.3	0.001
	-0.4 (-0.6–-0.3)	-5.4 (-7.5–-3.8)	
0–2h	-0.6±0.5	-15.8±4.4	0.001
	-0.5 (-1.4–0.05)	-17.5 (-19.6–-7.4)	
0–24h	-0.8±0.6	-48.5±1.9	0.001
	-0.8 (-1.8–-0.2)	-47.6 (-53–-47.2)	
2–24h	-0.25±0.6	-32.6±4.01	0.001
	-0.34 (-1.03–0.51)	-30.7 (-40.6–-29)	

*Mann-Whitney U test ($p<0.05$). KIM-1: Bioassay Technology Laboratory E0549Ra, Rat kidney Injury Molecule-1; NGAL: Bioassay TechnologyE0762Ra, Rat neutrophil gelatinase associated lipocalin; SD: Standard deviation; Min: Minimum; Max: Maximum.



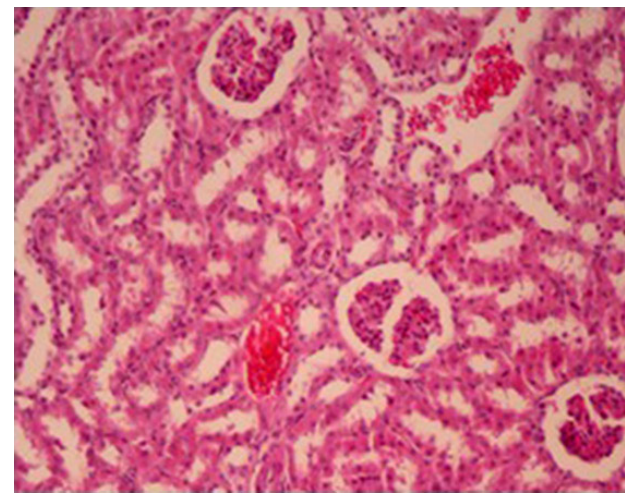


Figure 5. (a, b) Evaluation of serum kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin for the diagnosis of acute kidney injury. Receiver operating characteristic curves were drawn with the data of these markers from all rats.

Recent studies suggest that new biomarkers such as KIM-1 and NGAL show promising results for quantitative definition of AKI.[10,11] The downstream proteomic analyses show that after experimental nephrotoxic and ischemic injury in plasma and urine, NGAL levels were significantly increased.[12–14] A special weight-drop device developed by Marklund et al.[20]

Table 4. Diagnostic performance of KIM-1 and NGAL at 24h

	AUC	p-value	Cut-off	Sensitivity	95% Lower CI	95% Upper CI	Specificity	95% Lower CI	95% Upper CI
KIM1	1.000	<0.001	0.965	100.0	63.1	100.0	100.0	59.0	100.0
NGAL	1.000	<0.001	4.752	100.0	63.1	100.0	100.0	59.0	100.0

*Sensitivity, specificity, and predictive values were calculated for the cutoff, which represented the best discrimination as derived from the receiver operating characteristic curves (ROC). The area under the receiver operating characteristic curves (AUC), confidence interval (CI). KIM-1: Bioassay Technology Laboratory E0549Ra, Rat kidney injury molecule; NGAL: Bioassay Technology E0762Ra, Rat neutrophil gelatinase associated lipocalin.

and modified with lighter weight and shorter height by Kural et al.[21] was used to deliver a standard diffuse traumatic injury. There are several experimental rat models for mimicking the brain injury in humans. The acceleration model was one of them and it was chosen in our earlier brain trauma model study,[20,21,24] and after mild TBI, we investigated AKI findings histopathologically and NGAL, KIM-1 levels in plasma. Our results showed that both plasma NGAL and KIM-1 levels were significantly increased after trauma group at both 2 and 24 h. We also measured both markers' sensitivity and specificity for diagnosis of AKI.

NGAL is one of the most promising new markers to diagnose AKI. In contrast to pCrea and urinary output, which are measures of kidney function, NGAL is particularly induced in the injured nephron and then released into blood and urine, where it can be easily measured.[25]

Another study showed that, following obstructive nephropathy within 72 h, urinary NGAL and KIM-1 levels had a good accuracy to diagnose AKI. When the GFR is reduced by 50%, then the sCrea level can increase slightly, but the sCrea levels cannot reach a stable state within a short period.[26] NGAL concentration increases both in urine and plasma after 2 h. This increase was earlier than serum and plasma creatinine levels increase. Therefore, SCr cannot be used as a marker to accurately reflect short-term changes in renal function.[16] Recent studies show that serum cystatin C levels are more reliable and a more accurate test of kidney function than a creatinine test. When we compared serum cystatin C levels and creatinine levels, serum cystatin levels are less dependent on age, gender, and muscle mass then sCrea levels.[17–19] In addition, clinical studies have shown that NGAL is a strong predictor of poor clinical outcomes.[25–28]

A relation between NGAL and severe TBI has been noted previously.[29] On the other hand, plasma NGAL levels can increase without indicating AKI, but as a result of infection and sepsis. Increased NGAL levels are probably related with the severity of the systemic inflammatory responses, because of that it would be wise to support NGAL elevation by combining it with more kidney specific biomarkers for diagnosis of AKI. For instance, urinary and plasma biomarkers are cystatin C and KIM-1.[10,30,31]

We observed a statistically significant relation between mild and moderate TBI and serum KIM-1 levels. Serum KIM-1 levels were significantly correlated after 4 h following TBI. As such, the use of KIM-1 as an adjunct to other diagnostic tests such as NGAL may be benefi¬cial for early diagnosis of AKI after mild and moderate TBI.

Conclusion

The presence of AKI in patients with mild-to-moderate TBI increases the risk of mortality. Early diagnosis of AKI reduces the hospitalization period and requiring of dialysis. Diagnosis of AKI within 24 h with early biomarkers and starting therapy is crucial issues.

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Ethics Committee Approval: This study was approved by the Animal Care and Ethics Committee of Yeditepe University Faculty of Medicine (date: 01.03.2016; decision no: 524).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: Ş.T.N.; Design: Ş.T.N.; Supervision: Ş.T.N.; Materials: Ş.T.N., H.D.; Data: Ş.T.N., H.D.; Analysis: A.K., N.S.; Literature search: A.K., N.S.; Writing: Ş.T.N.; Critical revision: Ş.T.N., A.K., H.D., S.S.

Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZ*

Orta ve hafif beyin travmalı sıçanlarda böbrek fonksiyonlarının değerlendirilmesi

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AMAÇ: Acil servislerde sık olarak karşılaşılan beyin travmalı hastalarda, olguların tanı ve tedavisi sırasında olası akut böbrek hasarının (ABH) yeni biyokimyasal belirteçler eşliğinde erken tanısını koyarak, komplikasyonların önüne geçmeyi, tedavi süresini ve hastanın hastanede yatış süresini kısaltmayı amaçladık. Deney hayvanı kullanarak materyal metod açısından bilimsel sonuçlara ulaşabileceğimize karar verdik.
GEREÇ VE YÖNTEM: Çalışmamıza Wistard albino sıçanlar alındı. On beş sıçan rasgele üç gruba ayrıldı. Sham kontrol (n=1, sadece kraniyotomi), kontrol (n=7, sağlam), travma grup (n=7, kraniyotomiyi takiben beyin travması).
BULGULAR: Plazma kreatinin seviyelerinde 0. ve 24. saatlerde istatistiksel olarak anlamlı fark bulunamadı (sırasıyla, 0.35±0.02, 0.33±0.03, p>0.05). Her iki grubun plazma NGAL ve KIM-1 konsantrasyonlarında belirgin istatistiksel anlamlılık vardı (Friedman p<0.05). NGAL ve KIM-1 konsantrasyonlarının zamana göre karşılaştırılmasında (0 saat [s]-2s, 0s-24s, 2s-24s) belirgin istatistiksel anlamlılık vardı (Wilcoxon p<0.001, Bonferroni düzeltmesinden sonra).
TARTIŞMA: Hafif ve orta beyin travması olan hastalarda ABH'nın varlığı mortaliteyi artırmaktadır. ABH'nın ilk 24 saat içerisinde tanısının erken biyobelirteçlerle konularak tedaviye başlanması hayati önem taşımaktadır.
Anahtar sözcükler: Akut böbrek hasarı; böbrek hasar molekülü -1; nötrofil jelatinaz ilişkili lipokalin.

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