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ORIGINAL ARTICLE

Renal artery flow alterations in neonates with hypoxic ischemic encephalopathy

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Abstract

Background To compare kidney blood flow and kidney function tests in infants with hypoxic ischemic encephalopathy (HIE), and the effects of therapeutic hypothermia (TH) during the first 7 days of life.

Methods Fifty-nine infants with HIE were prospectively evaluated. Infants with moderate-severe HIE who required TH were classified as group 1 ($n=36$), infants with mild HIE were classified as group 2 ($n=23$), and healthy infants were classified as group 3 ($n=60$). Kidney function tests were evaluated on the sixth hour, third and seventh days of life in Group 1 and Group 2, and on the sixth hour and third day of life in group 3. Renal artery (RA) Doppler ultrasonography (dUS) was performed in all infants on the first, third, and seventh days of life.

Results Systolic and end diastolic blood flow in RA tended to increase and RA resistive index (RI) tended to decrease with time in group 1 ($p=0.0001$). While end diastolic blood flow rates in RA on the third day were similar in patients with severe HIE and mild HIE, it was lower in patients with mild-moderate-severe HIE than healthy newborns. On the seventh day, all three groups had similar values ($p>0.05$). Serum blood urea nitrogen (BUN), creatinine, uric acid, and cystatin C levels gradually decreased and glomerular filtration rate (GFR) gradually increased during TH in group 1 ($p=0.0001$). Serum creatinine levels gradually decreased while GFR gradually increased during the study period in group 2.

Conclusions Therapeutic hypothermia seems to help restore renal blood flow and kidney functions during the neonatal adaptive period with its neuroprotective properties.

Keywords Asphyxia · Hypothermia · Renoprotective · Newborn

Introduction

Perinatal asphyxia is defined as impaired blood flow or gas exchange to fetus before, during, or after birth which causes hypoxia, hypercapnia, and acidosis. Hypoxic ischemic encephalopathy (HIE) results from perinatal asphyxia [1]. Neonatal acute kidney injury (AKI) accompanies approximately 40% of HIE cases and causes worse clinical outcomes [2]. Renal hypoperfusion results in ischemia, acidosis, decreased GFR with impaired sodium and water reabsorption [3]. Animal studies demonstrated that reactive oxygen species, vasoconstriction, inflammation, intravascular coagulation, and disrupted microcirculation result in progressive post-ischemic reperfusion damage [4, 5], but less is known about kidney blood flow alterations in response to asphyxia.

The only neuroprotective treatment modality for moderate-severe HIE is therapeutic hypothermia (TH). The underlying mechanism suggested to be responsible for reduced ischemic tissue damage by hypothermia is its effect on

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cellular metabolism [6, 7]. A recent meta-analysis concluded that TH is also a renoprotective treatment [8]. However, to the best of our knowledge, there is no current data about the effects of TH on blood flow of other organ systems or if it has favorable impact on organ systems other than the brain.

In this study, the kidney blood flow of newborns with HIE and AKI development were evaluated.

Materials and methods

A total of 85 patients (inborn and transferred from different hospitals), gestational age 36 weeks and above, less than 6 h of age, and hospitalized in the Dr Sami Ulus Maternity and Children Training and Research Hospital with the diagnosis of perinatal asphyxia, were prospectively included in the study. This study was planned as a prospective cohort study (July, 2012, to July, 2013); therefore, all patients who were eligible during this time period were included. According to American College of Obstetrics and Gynecology (ACOG) definitions, perinatal asphyxia was diagnosed. [The guidelines of the ACOG consider the following criteria in diagnosing asphyxia: *Major criteria*: 1. metabolic acidosis in umbilical arterial blood (pH < 7.00 and base deficit ≥ − 12 mmol/L); 2. early-onset moderate-severe encephalopathy findings in newborns with a gestational age of ≥ 34 weeks; 3. cerebral palsy, the spastic quadriplegic or dyskinetic type; 4. exclusion of trauma, coagulation disorders, infections, and genetic diseases. *Additional criteria*: 1. sudden unexpected hypoxic event before or during delivery; 2. sudden fetal bradycardia, severe electronic fetal monitoring abnormalities; 3. APGAR fifth minute score of 0–3; 4. multisystem involvement (encephalopathy and at least one organ involvement) within 72 h of birth; 5. evidence of acute nonfocal cerebral anomaly by imaging methods] [9]. Patients older than 6 h of age; less than 36 weeks of gestational age; with major congenital malformations, chromosomal abnormalities, metabolic diseases, congenital viral infections, septic shock, and without parental consent were excluded. HIE stages according to the Sarnat and Sarnat staging scale [mild (stage 1), moderate (stage 2), severe (stage 3)] were evaluated by an experienced neonatologist for each patient 6 h after birth and repeated again every 6 h until the third day of life and the worst degree was concluded as final HIE stage.

Patients who were treated in the NICU with a diagnosis of moderate or severe HIE and received TH were defined as group 1 ($n = 36$), patients with mild HIE and who did not need TH were defined as group 2 ($n = 23$). In group 1, moderate HIE patients were defined as group 1a ($n = 16$), and severe HIE patients were defined as group 1b ($n = 20$). Gestational week, postnatal age, and sex-matched healthy newborns born in our institution were defined as group 3 ($n = 60$). Flow diagram of the study population is given in Fig. 1. Therapeutic hypothermia was applied with a Tecotherm device (Inspiration, Leicester, UK) as servo-controlled whole body cooling with a rectal temperature probe targeting a rectal temperature of 33.5 °C. Re-warming procedure lasting for 7 h was maintained in all cases following 72 h of cooling period and re-warming phase was terminated at the end of this period as soon as a rectal temperature of 36.5 °C was ensured.

BUN, creatinine, uric acid, and cystatin C levels in serum and $ß_2$ microglobulin levels in urine were obtained before initiation of TH (first day), on the third day (before the initiation of rewarming phase), and seventh day of life in moderate-severe HIE infants; on the first 6 h, and third and seventh days of life in mild HIE infants. Infants with moderate-severe HIE were followed up with their mothers and discharged from the hospital at postnatal 72 h; blood and urine samples were taken only in the first 6 h postnatally and on the third day before discharge. In order to determine the occurrence of AKI in moderate-severe HIE and mild-HIE, creatinine levels were also measured at the postnatal 24 h in all cases in addition to those collected on the sixth hour, and third and seventh days. Serum cystatin C levels were measured with ROCHE-P800® (Roche Diagnostic, USA) device using a photometric technique and urine β_2 microglobulin levels were measured with IMMAGE 800® (Beckman Coulter Inc, Brea, CA) device using a nephelometric method. GFR was calculated according to Schwartz formula [$k \times$ height (cm)/serum creatinine (mg/dL); k_{preterm}: 0.33; GA between $36^{0/6}$ and $36^{6/7}$ and k_{term}: 0,45; GA above $37^{0/7}$]. According to modified KDIGO (Kidney Disease: Improving Global Outcomes) classification for use in the neonatal period, enrolled subjects were classified for AKI stages after following their serum creatinine values (Table 1) [10]. Urine output criteria were dismissed because urine output could not be monitorized accurately.

A pediatric radiologist measured RA peak systolic flow velocity (PSV) and end diastolic flow velocity (EDV) with dUS (using Mindray M5 device (Portable Color Ultrasound System, Inc, USA) on the first day (before TH treatment), on the third day of TH (just before warming phase), and on day 7 in moderate-severe HIE infants; and in the first 6 h of life (day 1), postnatal day 3, and day 7 in mild-HIE infants and healthy infants. In group 3, the first measurements were made while the infants were in the hospital. Infants were called for control on the seventh day of life after discharge and dUS were performed. The findings were obtained by evaluating peak systolic flow velocity (Vs) and peak end diastolic flow velocity (Vd) from three waveforms with the highest amplitude after recording through 20–30 sequential constant beat rates. RI of RA is calculated according to the following formula (peak systolic flow rate − peak end diastolic flow rate/peak systolic flow rate). All patients were

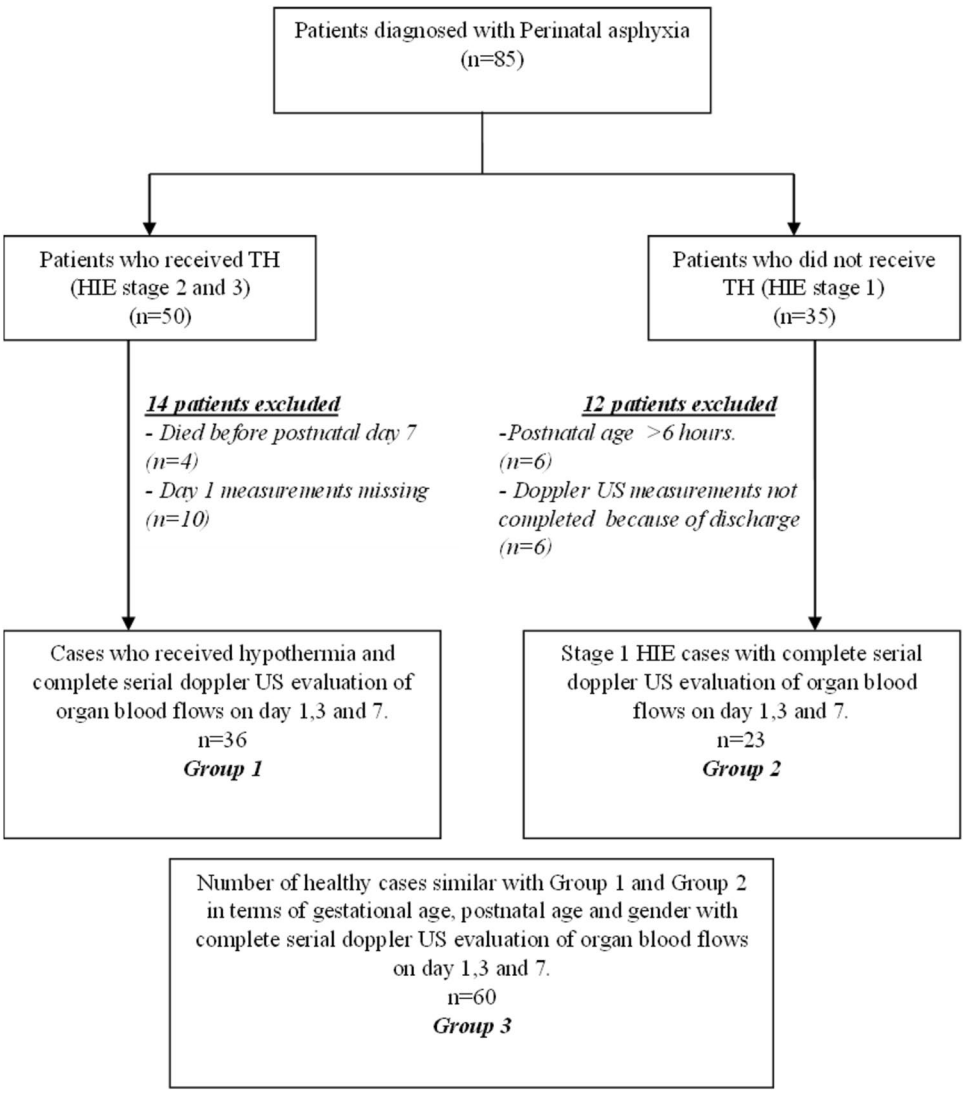

Fig. 1 Selection scheme of the study groups

Table 1 Neonatal modified version of KDIGO classification

Stage	Serum creatinine (SCr)	Urine output
0	No change in SCr or increase < 0.3 mg/dL	≥ 0.5 mL/kg/h
1	SCr increase ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 h, or SCr increase ≥ 1.5–1.9 × reference SCr within 7 days	< 0.5 mL/kg/h for 6–12 h
2	SCr increase ≥ 2.0–2.9 × reference SCr	< 0.5 mL/kg/h for ≥ 12 h
3	SCr increase ≥ 3 × reference SCr, or SCr ≥ 2.5 mg/dL (≥ 221 µmol/L), or receipt of dialysis	< 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h

assessed by the same pediatric radiologist who was blinded for the medical history.

Clinical findings, hospital mortality and requirement of mechanical ventilation, continuous positive airway pressure ventilation, supplementary oxygen, inotropic drugs, and dialysis were also recorded.

The study protocol was approved by the local ethical committee (Keçiören Training and Research Hospital, approval number: 327/2013). Parental consent was obtained for all patients.

Statistical analysis

SPSS Patch 15 Program (SPSS Inc., Chicago, IL) was used for the statistical analysis of the data. Kolmogorov–Smirnov test was applied to assess the distribution

form of the variables. Mean ± SD for parametric variables and median (minimum–maximum) values were declared. In order to establish the relation between variables, Pearson for parametric variables and Spearman correlation for non-parametric variables were implemented. Student *t* test for parametric variables and Mann–Whitney U test for non-parametric variables were used for the comparison of constant variables between two independent groups. Paired sample test for parametric variables and Wilcoxon test for non-parametric variables were applied for the comparison of constant variables between two dependent groups. Chi-square test (X^2) for the comparison of categorical variables was used. Grenhouse-Geisser correction was established for parametric data for the analysis of repeated findings by using repeated measures ANOVA test in the dependent group and the alteration of repeated data over time was determined by using Bonferroni correction. Friedman analysis was used for non-parametric repeated data. Differences among three groups were analyzed by one-way ANOVA or Kruskal–Wallis tests ($p > 0.05$). Results with $p < 0.05$ were considered statistically significant.

Results

The demographic and clinical characteristics of the study group are given in Table 2.

Comparison of the dUS data of the groups

In both infants with moderate-severe HIE and infants with mild HIE, RA-PSV and RA-EDV tended to increase over time, while RA RI tended to decrease. In the control group RA-PSV and RA-EDV tended to increase over time.

When RA blood flow measurements were compared, RA-PSV were similar in all three groups at day 1. On the third and seventh days, RA-PSV was found to be higher in infants with moderate-severe HIE. RA-EDV was found to be lower on day 1 in infants with moderate-severe HIE. On the third day, RA-EDV of healthy subjects were higher than those of moderate-severe HIE and mild HIE. On the seventh day, moderate-severe HIE, mild HIE, and RA-EDV levels in healthy infants were similar.

Healthy infants had lower RA RI on the first, third, and seventh days. On the first day RA RI was found to be higher in infants with moderate-severe HIE compared to infants with mild HIE and healthy subjects. There was no statistically significant difference between infants with moderate-severe HIE and infants with mild HIE on the third and seventh days (Table 3; Fig. 2).

Comparison of biochemical kidney function tests of the groups

BUN, creatinine, uric acid, and cystatin C levels were gradually decreased and GFR was gradually increased during TH in infants in the moderate-severe group ($p = 0.0001$). In the mild HIE group, GFR increased gradually, while other kidney functions remained within the normal range. Cystatin C levels were lower in the healthy group than in the mild HIE group on the seventh day ($p = 0.003$) (Table 4; Fig. 3). Cystatin C levels were significantly different between the groups on the third day. Urine ß2 microglobulin levels were significantly higher

Table 2 Comparison of demographics and clinical details of the groups

	Group 1 ($n = 36$)	Group 2 ($n = 23$)	Group 3 ($n = 60$)	*p* value
Gender (female/male) (*n*/%)	17 (52.8%)/19 (47.2%)	10 (43.5%)/13 (56.5%)	33 (55%)/27 (45%)	0.579
Gestational age (week)	39 (36–41)	39 (36–41)	39 (37–41)	0.123
Birth weight (g)	3059 ± 500	3359 ± 515	3274 ± 518	0.057
Mode of delivery (CS) (*n*/%)	22 (61.1%)	15 (65.2%)	(60%)	0.908
APGAR score (5 min)	5 (0–7)	8 (5–9)	10 (10–10)	0.0001
Maternal age (years)	28 (18–38)	26.2 ± 6.3	26 (19–40)	0.413
Mechanical ventilation (*n*/%)	33 (91.7%)	3 (13%)	-	0.0001
Duration of mechanical ventilation (day)	5 (2–21)	4.5 (4–5)	-	0.813
CPAP (*n*/%)	23 (65.7%)	7 (30.4%)	-	0.009
Duration of CPAP (day)	2 (1–13)	2 (1–7)	-	0.894
Oxygen (*n*/%)	26 (74.3%)	20 (87%)	-	0.233
Duration of oxygen (day)	2 (1–10)	2 (1–5)	-	0.235
Inotropic agent (*n*/%)	24 (66.7%)	2 (8.7%)	-	0.0001
Duration of inotropic agent (day)	3 (2–9)	2.5 (2–3)	-	0.339
Duration of hospitalization (day)	19.5 (7–70)	8 (7–21)	-	0.0001
Hospital mortality (*n*/%)	5 (13.9%)	0 (0%)	-	0.022

Table 3 Renal artery peak systolic flow velocity (PSV), end diastolic flow velocity (EDV), and resistivity index (RI) measurements in all groups

	Days	Group 1 ($n=36$)	Group 2 ($n=33$)	Group 3 ($n=60$)	p	$p_{1\text{-}2}$	$p_{2\text{-}3}$	$p_{1\text{-}3}$
RA PSV (cm/s)	**1**	30.9 ± 9.3	29 (23–39)	28.3 ± 5.2	0.135	0.398	***0.029***	0.534
	3	37.4 ± 7.1	36.2 ± 7.7	33.3 ± 6.8	***0.030***	0.933	0.360	***0.040***
	7	42.5 ± 7.2	39 ± 8.1	35.3 ± 7.1	***0.0001***	0.332	0.231	***0.0001***
RA EDV (cm/s)	**1**	8.5 ± 3.0	9 (5–13)	11 (5–19)	***0.005***	0.282	0.101	***0.002***
	3	9 (6–13)	10.4 ± 3.2	12 ± 2.9	***0.005***	0.842	***0.026***	***0.003***
	7	11.9 ± 2.8	11.6 ± 3.2	13.3 ± 3.2	0.060	0.988	0.162	0.148
RA RI	**1**	0.81 ± 0.07	0.74 ± 0.10	0.61 (0.51–0.71)	***0.0001***	***0.019***	***0.0001***	***0.0001***
	3	0.71 ± 0.08	0.72 ± 0.10	0.59 (0.51–0.69)	***0.0001***	0.708	***0.0001***	***0.0001***
	7	0.68 ± 0.09	0.68 ± 0.06	0.61 (0.51–0.78)	***0.0001***	0.484	***0.0001***	***0.0001***

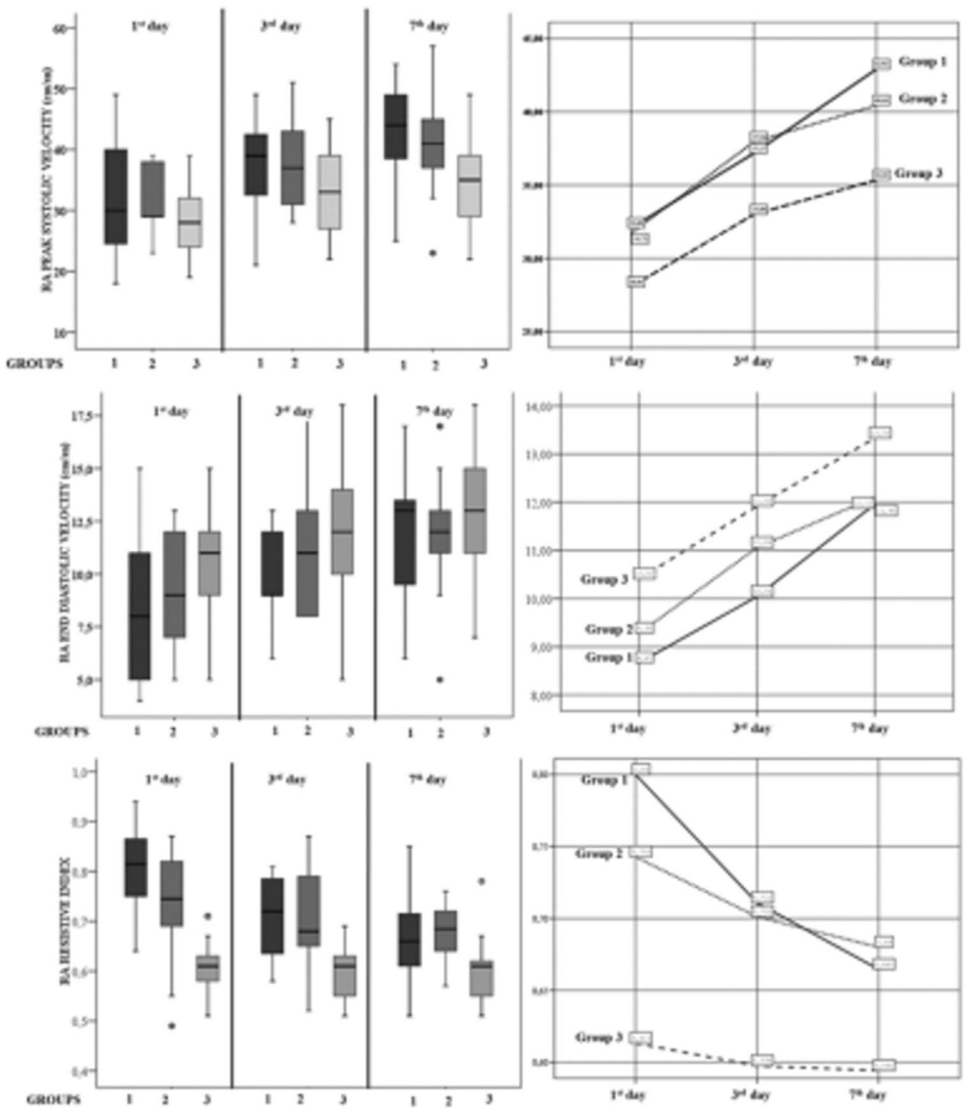

Fig. 2 Comparison of systolic and end diastolic flow rates in RA and RA RI for three different days between group 1, group 2, and group 3, and alterations in time among all groups

in the HIE group on the first postnatal day compared to healthy newborns, and urine ß2 microglobulin levels in healthy subjects were lower on the first day compared to the third day. Urine ß2 microglobulin levels were found to decrease within days, although not statistically significant, in the moderate-severe HIE and mild HIE groups. On the third day, urinary ß2 microglobulin levels in all 3 groups were found to be similar (Table 4).

Table 4 Comparison of kidney function tests including BUN, creatine, uric acid, B2 microglobuline, cystain C, on the 1st, 3rd, and 7th days

	Days	Group 1 ($n=36$)	Group 2 ($n=23$)	Group 3 ($n=60$)	F/X^2	p	p_{1-2}	p_{2-3}	p_{1-3}
BUN (mg/dL)	**1**	10 (4–24)	9.8 ± 5.1	8.5 ± 2.9	6.132	***0.047***	0.328	0.345	***0.012***
	3	21 ± 9.2	8.9 ± 5.6	6.7 ± 3.3	61.335	***0.0001***	***0.0001***	0.357	***0.0001***
	7	11 (5–48)	7.4 ± 6.1			***0.0001***			
Creatinine (mg/dL)	**1**	0.99 (0.49–2.10)	0.88 ± 0.19	0.73 ± 0.17	31.043	***0.0001***	***0.046***	***0.002***	***0.0001***
	3	0.78 (0.30–2.30)	0.52 ± 0.16	0.42 ± 0.16	41.307	***0.0001***	***0.0001***	***0.011***	***0.0001***
	7	0.44 (0.2–2.0)	0.47 ± 0.18			0.906			
GFR	**1**	23.49 ± 7.22	27.05 ± 7.88	32.51 ± 7.93	15.715	***0.0001***	0.230	***0.018***	***0.0001***
	3	31.47 ± 14.05	46.07 ± 12.7	62.38 ± 33.63	16.274	***0.0001***	0.0001	***0.012***	***0.0001***
	7	52.27 ± 20.18	53.29 ± 24.19			0.866			
Uric acid (mg/dL)	**1**	7.9 ± 1.7	6.3 ± 1.5	5.4 ± 1.1	36.801	***0.0001***	***0.0001***	***0.028***	***0.0001***
	3	5.5 ± 2.3	3.2 ± 1.3	3.1 ± 1.1	25.227	***0.0001***	***0.0001***	0.952	***0.0001***
	7	3.2 ± 1.4	2.7 ± 0.7			0.235			
B_2 microglobulin mg/dL Cr	**1**	28.7 (1.79–281.5)	19.6 (1.2–194)	4.1 (0.18–38.8)	9.651	***0.008***	0.456	***0.017***	***0.002***
	3	37.2 (2.1–206)	21.3 (6.5–435)	21.3 ± 18.9	5.060	0.080	0.780	0.126	***0.030***
	7	51.2 (3.8–256)	40.3 (4.5–180.4)			0.810			
Cystatin C (mg/L)	**1**	1.86 ± 0.47	1.72 ± 0.26	1.92 ± 0.29	2.437	0.092	0.391	0.093	0.687
	3	1.53 ± 0.32	1.61 ± 0.28	1.72 ± 0.22	6.056	***0.003***	0.576	0.358	***0.006***
	7	1.39 ± 0.41	1.67 ± 0.24			***0.003***			

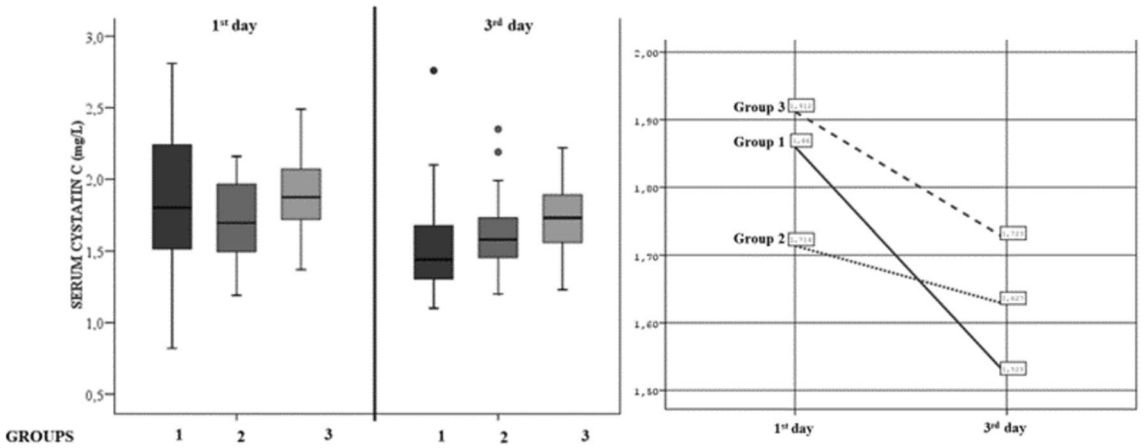

Fig. 3 Comparison of serum cystatin C levels for different days between group 1, group 2, and group 3, and alterations in time among all groups

KDIGO classification was used to evaluate AKI in all patients with HIE. In staging, the change in serum creatinine levels over time obtained from serial measurements in the first 7 postnatal days was evaluated. Fifty-one (86.4%) of 59 patients (infants with HIE) had no AKI, six (10.2%) developed stage 1 AKI, and two (3.4%) developed stage 2 AKI. Stage 3 AKI was not observed in any of the infants. When the rates of AKI were evaluated according to the HIE stage, 19 (86.4%) of the mild HIE patients ($n=22$) did not develop AKI, and three (13.6%) developed stage 1 AKI. Sixteen (94.1%) of the patients with moderate HIE ($n=17$) did not develop AKI, and one (5.9%) developed stage 1 AKI; 16 (80%) severe HIE patients ($n=20$) did not develop AKI; two (10%) developed stage 1 AKI; and two (10%) developed stage 2 AKI. The AKI stages of patients with mild HIE and patients with moderate-severe HIE requiring TH were statistically insignificant. When the RA RI of HIE patients were compared according to the AKI stage, no statistically significant difference was found.

Five of 36 patients (13.9%) with moderate-severe HIE died prior to discharge from NICU despite treatments. The mortality rate of patients with severe HIE was significantly higher than patients with moderate HIE ($p=0.011$). When kidney function test results on the first day of life were compared between patients who survived or not, no statistically significant difference was observed. Renal blood flow rate

determined by dUS on the first day of life was evaluated for the patients who could and could not survive and systolic blood flow on RA was found to be lower in patients who could not survive [median 21 cm/s (18–23) vs. mean 32.4 ± 8.9 cm/s; $p = 0.019$]. Also, RI of RA was higher in patients who could not survive [median 0.89 (0.77–0.94) vs. 0.080 ± 0.07; $p = 0.014$].

Discussion

Tissue reperfusion after hypoxic-ischemic insult not only leads to neuronal damage but also causes damage to the other organ systems. In our study, infants with HIE (mild, moderate, and severe) and healthy infants had similar RA systolic blood flow rates on the first postnatal day; in infants with mild HIE, RA systolic and end diastolic blood flow velocities tended to increase and RI values tended to decrease over time; RA systolic and diastolic blood flow velocities gradually increased and RI values gradually decreased in infants with moderate-severe HIE; and RA RI was highest in infants with moderate-severe HIE. Also, BUN, creatinine, uric acid, and cystatin C levels gradually decreased and glomerular filtration rate (GFR) gradually increased in infants with moderate-severe HIE.

Pokharel et al. [11] evaluated renal arterial blood flow velocities and RIs in 16 preterm infants in the first seven postnatal days and 23 term infants in the first five postnatal days. They showed that systolic and end diastolic blood flow velocities increased significantly in preterms, especially between the third and fifth days of life, whereas systolic blood flow velocity remained constant in term newborns, and end diastolic blood flow velocity increased; they suggested that this difference was due to higher cardiac output in preterms compared to term newborns. In our study, it was observed that renal artery systolic and end diastolic blood flow velocities of healthy term newborns evaluated in the first seven postnatal days tended to increase gradually from birth. Meneza et al. [12] evaluated 27 infants with HIE and 14 healthy infants and showed that renal artery systolic and end diastolic blood flow velocities were lower and renal artery RI were higher in infants with HIE on the first day of life. Ramaswamy et al. [13] found that renal artery end diastolic blood flow velocities were lower in infants with HIE who developed AKI on the first and third days of life compared to healthy newborns. Luciano et al. [14] compared the renal blood flow of newborns with severe HIE without TH and healthy newborns. They demonstrated lower mean RA systolic blood flow rate on the first day of life in HIE patients who experienced AKI defined as plasma creatinine concentration > 1.3 mg/dL (> 123 mol/L) lasting for at least 2 consecutive days. They also found that mean RA systolic blood flow rates on the third day have similar patterns with the first day. Ilves et al. [15] studied organ blood flow with dUS in newborns with HIE and found that RA blood flow remained unchanged in the first 12 h after asphyxia in newborns with mild to moderate HIE with a progressive decline, thereafter reaching the lowest levels on the second day of life. Reduced renal blood flow during the first day of life was found to be a significant risk factor for AKI development. In our study, RA systolic blood flow rates were similar in newborns with mild and moderate-severe HIE in comparison with healthy newborns. However, as aortic blood flow rates were not evaluated, we cannot explain why systolic blood flow rate did not alter in relation to HIE severity. While no statistically significant difference was observed for end diastolic blood flow rate in newborns with mild HIE in comparison with healthy newborns and moderate-severe HIE, significantly lower values were encountered in newborns with moderate-severe HIE than healthy newborns. RA systolic and end diastolic blood flow rates tended to increase and RI tended to decrease with time in newborns with mild HIE. To the best of our knowledge, there is no study comparing how renal blood flow changes in response to TH. In our study, we observed a gradual decrease in RA systolic and end diastolic blood flow rates and a gradual decrease in RI in infants with HIE who received TH. Meanwhile, RA end diastolic blood flow rates on the third day were found similar in the severe and moderate HIE subgroups but found to be lower in mild and severe/moderate HIE subgroups than healthy newborns; no significant difference was observed on the seventh day among the three groups. It was thought that renal artery flows in infants who received TH had a resemblance to the normal physiological adaptive process.

A few studies in the literature report elevated $ß_2$ microglobulin levels in perinatal asphyxia. Cai et al. [16] evaluated kidney functions of 60 newborns with HIE and found elevated $ß_2$ microglobulin levels on the first, third, and seventh days of life in comparison with healthy newborns with the peak levels reached on the third day. Aggarwal et al. [17] studied kidney functions of 25 newborns with HIE and found elevated urinary $ß_2$ microglobulin in comparison with healthy newborns. Zhang et al. [18] found that serum Cys-C, β2-microglobulin, urine NGAL, and α1-microglobulin are early specific indicators for the diagnosis of kidney injury after neonatal asphyxia. Consistently, we found elevated urinary $ß_2$ microglobulin levels on the first day of life in newborns with HIE in comparison to healthy newborns. Urinary $ß_2$ microglobulin levels were similar at the beginning and at the end of hypothermia sessions but highest at the seventh day in our study. Urinary $ß_2$ microglobulin levels on the third day were higher than the first day in healthy newborns. This might be attributed to the physiologic process in which diuresis is enhanced and tubular functions maturate. Cystatin C is another marker for kidney damage. A limited number of studies evaluating relationships of kidney functions of

newborns with perinatal asphyxia and cystatin C report that serum cystatin C levels are significantly higher in newborns with perinatal asphyxia and cystatin C is a good marker to predict AKI [19, 20]. We observed significant decreases in serum cystatin C levels on the third and seventh days in comparison with the first day in infants with moderate-severe HIE.

In a recent meta-analysis, it was shown that TH is renoprotective, while there is considerable heterogeneity in AKI definitions. Presence of oliguria was used in five of the studies and increased creatinine level was used in seven studies for the AKI definition included in this meta-analysis [8]. Since there are discrepant definitions in the studies, a universal definition of AKI, e.g., a modified KDIGO definition for neonatal use, would be more reliable not only for incidence of AKI in HIE patients but also for evaluation of renoprotective effects of TH. In their randomized controlled trial, Tanigasalam et al. [21] compared 120 patients with and without TH and demonstrated that TH reduced the incidence and severity of AKI in asphyxiated term neonates, according to Acute Kidney Injury Network criteria. Similarly, Selewski et al. [22] retrospectively evaluated 96 term newborns who received TH, and according to Modified AKI Network criteria, they found AKI in 38% of the patients. Robertsson Grossman et al. [23], who studied AKI in HIE infants treated with TH using the KDIGO definition modified for use in neonatal patients, found that the rate of AKI was 45% and the stage of AKI correlated with the degree of HIE. Chock et al. [24] retrospectively evaluated 38 newborns who received TH and measured renal saturation levels using continuous kidney near-infrared spectroscopy monitoring during and after 24 h of TH. AKI was observed in 15 of 38 (39%) newborns with TH. In our study, six infants (10.2%) developed stage 1 AKI and two (3.4%) developed stage 2 AKI. None of the infants developed stage 3 AKI; this might be due to severe HIE patients being deceased before developing AKI or the beneficial effects of TH. If a comparison could be made in patients with moderate-severe HIE who did not receive TH, this result could be said more clearly. Since TH is the only treatment for moderate-severe HIE patients, it is not possible to make this evaluation and comparison. TH is proven to have positive effects on mortality and neurodevelopment. A recent Cochrane meta-analysis conducted in 2013 reports the mortality rate for newborns who received TH as 29.7% [8]. In our study, the mortality rate in newborns who received TH was 13.9%. Neonates who died had lower RA systolic blood flow rates and higher RA RI values on the first day. According to these data, if those infants had survived, perhaps stage 3 AKI would have developed in subsequent days. During our study period, mortality rate in newborns who received TH was 13.9%; this might be attributed to early initiation of TH treatment.

A strength of our study is the large number and diversity of patients in the cohort. The study included affected/unaffected patients to different degrees, such as babies with moderate-severe HIE receiving TH, babies with mild HIE, and healthy controls. Another strength of the study is the evaluation of renal blood flows on the first, third, and seventh days of life supported by biochemical markers. A limitation of our study is that neonates with AKI were likely missed since urine output criteria for KDIGO were not assessed. This might have enabled us to find the true incidence of AKI in our cohort. Another limitation of our study is the lack of long-term follow-up data regarding these babies.

In conclusion, with the previous data suggesting neuroprotective effects, TH might also help renal blood flow to facilitate normal physiological adaptive processes. Long-term follow-up clinical studies are needed.

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Author contribution All the authors have made a substantial contribution to the design of the study, the collection of data or the analysis and have been involved in the writing of the article were included in the list of authors.

Declarations

Conflict of interest The authors declare no competing interests.

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