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Effects of total parenteral nutrition on renal function in preterm neonate

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Summary

Aim: The aim of this study was to establish serum sistatine C, urine β_2 microglobulin, gluthatione-S -transferase π and N-acetyle β-D glucosaminidase levels in order to evaluate the effect of total parenteral nutrition on renal function in premature infants. In addition, we aimed to compare the renal functions between premature infants receiving total parenteral nutrition and control groups receiving enteral feeding.

Material and Method: A hundred four premature infants with a gestational age between 28 and 34 weeks were included in the study. The parenteral nutrition group consisted of 50 infants (male/female; 23/27 and mean weight 1258±212.3 g) and the enteral nutrition group consisted of 54 infants (male/female; 20/34 and mean weight 1608±206.1 g). In the parenteral nutrition group; total parenteral group nutrition was initiated on the 3rd day in the enteral nutrition group, minimal enteral nutrition was started on a mean of 6.3±2.4 days and total enteral nutrition was started on a mean of 24.5±6.3 days. Breastmilk was given orally or by orogastric/nasogastric tube at first day of life in the enteral group. On the 3rd and 30th day of life, blood samples of all patients were obtained for evaluating biochemical parameters and cystatin C and urine samples were obtained for evaluation of N-acetyl β-D glucosaminidase, gluthatione-S-transferase π, β_2 microglobulin, sodium, creatinin levels, density and pH of the urine. The study was approved by the ethics commite (2008/16).

Results: When we compared the patients who received total parenteral nutrition and enteral nutrition on the 3rd and 30th days, serum cystatin C, urinary β_2 microglobulin, gluthatione-S-transferase π and N-acetyl- β-D glucosaminidase excretions were similar on the 3rd day however were significantly higher on the 30th day in samples of the patients receiving total parenteral nutrition ($p<0.05$ for each parameter on each day).

Conclusions: This study shows that total parenteral nutrition in premature infants can have adverse effects on glomerular and tubular functions of the kidney which can be manifested at an early time with cystatin C, β_2 microglobulin, gluthatione-S-transferase π and N-acetyl β-D glucosaminidase. *(Turk Arch Ped 2012; 47: 244-249)*

Key words: Cystatin C, gluthatione-S-transferase π, N-acetyl β-D glucosaminidase, preterm, renal function, total parenteral nutrition, β_2 microglobulin

Introduction

The neonatal period is a transition period during which the organism adapts itself from the intrauterine life to the external environment. Since body functions of the newborns have not developed fully yet in this period, physiologic and biochemical changes involving all systems occur. Premature delivery is defined as birth of the baby before the 37th week starting with the first day of the last mensturation (1). Although the number of the nephrons reach a normal value after the 32nd week, they are short and functionally immature; the development of renal vessels is not completed and renal blood flow is very low (2). Therefore, disruption of renal functions in newborns is easier. Especially in preterm infants, inadequate maturation of the kidneys causes more rapid disruption of renal functions and intensive treatment with dextrose, electrolyte, lipid and protein fluids given by total parenteral nutrition leads to an additional load for the kidneys of the preterm infant.

In many studies performed in recent years, it has been reported that serum cystatin C, urinary N-acetyl- β-D glucosaminidase (NAG), β2 microglobulin (β2M) and glutathione-S-transferase π (GST π) show glomerular, proximal and distal tubular damage in the kidneys in the early period (3,4,5,6,7,8).

In this study, we aimed to investigate the effects of TPN on the kidneys by comparing renal glomerular and tubular functions in preterm infants who received TPN and who were fed enterally.

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Material and Method

This prospective study included 104 preterm patients with a gestational age between 28 and 34th who were treated after hospitalization in Preterm Intensive Care Unit in Clinic of Pediatrics, İnönü University Medical Faculty, Turgut Özal Medical Center between January 2007 and July 2008. 50 patients who received total parenteral nutrition (male/female: 23/27) and 54 patients who were fed enterally (male/female: 20/34) were included in this study. The gestational age was determined by Ballard scoring system. In this study, the gestational age was expressed as gestational weeks and birth weight was expressed as grams. The mode of delivery, gender, height, body weight, presence of respiratory distress syndrome (RDS), presence of early neonatal sepsis/late neonatal sepsis and use of aminoglycosides were evaluated. In addition, it was determined if the mother had conditions including premature rupture of membranes (PRM), urinary tract infection, preeclampsia/eclampsia and diabetes mellitus (DM). Patients whose total parenteral nutrition was started before the third day, who were lost in the early period and thus in whom serum and urine could not be collected adequately, who received TPN for less than 10 days because of any reason and who had underlying urinary anomaly, cardiac anomaly including patent dustus arteriosus (PDA) or who were clearly syndromic were not included in the study.

For this study "Ethics Committee Approval with the number 2008/16 was obtained from İnönü University Ethics Committee and informed consent was obtained from the families of all patients in accordance with Helsinki Decleration reviewed in 2008.

Biochemical variables

In the study, TPN was started on the third day in all infants in the TPN group (9). Only dextrose was started on the first day in all patients according to blood glucose monitoring. 2-4 mEq/kg/day sodium was added to dextrose on the second and third days. After the third day serum and urine samples were collected and protein (1 g/kg/day) and lipid (0.5 g/kg/day) supplements were started. Protein and lipid content was increased by 0.5-1 g/kg/day to reach 3.5 g/kg/day on the seventh day of hospitalization. Glutamine, vitamin or trace elements were not added to TPN in this group. In addition, additinal enteral products were not given to the patients who were fed enterally. Serum and urinary samples were recollected on the 30th day from the patients who were given TPN and who were fed enterally and the study was performed with these variables. Venous blood samples were obtained from the patients who were given TPN and who were fed enterally to measure serum cystatin C, glucose, BUN, creatinine, uric acid, total protein, albumin, AST, ALT, ALP, sodium, potassium, calcium and phosphorus. Biochemical data were tested immediately, whereas the blood sample for cystatin C was centrifuged immediately after collection and kept at -70 Cº. Urinary samples were obtained to determine N-acetyl glucosaminidase, GST π, β2M, Na, creatinine, density and pH. β2microglobulin, Na, creatinine, pH and density were tested immediately after obtaining the urine sample. For N-acetyl glucosaminidase and GST π the urine samples were kept at -70 Cº in the refrigerator and the tests were done later (in three months) using the following methods:

Cystatine C and B2 microglobulin were tested by nephelometric method with N Latex Cystatine C kit and N Latex microglobulin kit in Dade behring Marburg GmbH, Germany model analyzer.

GST π was tested by microelisa method with immunodiagnostic kit using Brio Seac Radium company 50041 (Italy) device.

N-acetyl β-D glucosaminidase was tested spectrophotometrically by calorimetric method against a calibrator with a wavelenght of 505 nm with diazyme kit using Shimadzu UV-1201V Spectophotometer Siemens device.

Statistical Analyses

Statistical analyses were done using Scientific Package for Social Scienses (SPSS) computer package program. Considering the structure of the data obtained chi-square test (in comparison of groups for numeric data), Paired t test (for dependent and interval variables), Student t test (for independent and interval variables) and Mann-Whitney-U test were used. P value was given for all tests and a p value of <0.05 was considered to be significant.

Results

Demographic and clinical data

A total of 104 premature infants with a gestational age ranging between 28 and 34 gestational weeks were included in this study. 50 of these patients were receiving TPN (male/female: 23/27, mean height: 36.9±2.7 cm and mean weight: 1258±212.3 g) and 54 were being fed enterally (male/female: 20/34, mean height: 40.9±2.2 cm and mean weight: 1608±206.1 g). There was no significant difference between the two groups in terms of respiratory distress syndrome (RDS), early or late neonatal sepsis or use of aminoglycosides ($p>0.05$). In the TPN group, TNP was started after the third day. Minimal enteral feeding was started on the 24.5±6.3rd day. In the group who were fed enterally, breastmilk was started on the first day orally or by tube. The clinical and demographic data of all patients are given in Table 1.

Evaluation of the TPN group and the group who was fed enterally in terms of prenatal and perinatal maternal risk factors is shown in Table 2.

Biochemical data

When the group who was given total parenteral nutrition and who was fed enterally were compared, no significant difference was found in serum glucose, BUN, total protein and uric acid values on both the third and 30th day. Serum Na, Ca and creatinine values on the third day were found to be significantly increased in the patient group ($p<0.005$), whereas

no difference was found between the values on the 30th day. Serum albumin, AST, ALT, ALP, phosphorus, K and cystatin C values were not found to be significantly different on the third day, whereas they were found to be significantly increased in the patient group on the 30th day (p<0.001).

When the TPN group and the enteral feeding group were compared, urinary pH, density and creatinine values on the third and 30th day were not found to be significantly different. Urinary Na values on the third day were found to be significantly higher in the patient group (p<0.05). While there was no significant difference in serum cystatin C and urinary β 2M, GSTπ and NAG values on the third day, the values on the 30th day were found to be significantly higher in the patient group (p<0.001).

Evaluation of the TPN and the enteral feeding groups in terms of serum and urinary biochemical values is shown in Table 3 and serum cystatine C and urinary β2M, GSTπ, NAG values are given in Table 4.

Table 1. Demographic and clinical data of the patients

	Enteral n (%)	TPB n (%)	p
Gestational week			
28-30 weeks	8 (14.8)	40 (80)	<0.05
30-32 weeks	22 (40.7)	8 (16)	<0.05
32-34 weeks	24 (44.5)	2 (4)	<0.05
Birth weight (g)	1608±206,1 g	1258±212,3 g	<0,01
750-1000 g	0 (0)	5 (10)	
1000-1250 g	3 (5)	18 (36)	
1250-1500 g	18 (34)	24 (48)	
>1500 g	33 (61)	3 (6)	
Gender (Female/Male)	34 (63)/20 (37)	27 (54)/23 (46)	>0.05
RDS	22 (44.4)	26 (52)	>0.05
Sepsis	39 (72.2)	40 (80)	>0.05
Use of Aminoglycoside	49 (90.7)	45 (90)	>0.05

RDS: Respiratory distress syndrome

Table 2. Maternal risk factors

	Enteral n (%)	TPB n (%)	p
UTI	10 (18.5)	10 (20)	>0.05
PRM	18 (33.3)	19 (38)	>0.05
HT	11 (20.4)	23 (46)	0.01
Preeclampsia	9 (16.7)	13 (26)	>0.05
Eclampsia	0 (0)	9 (18)	0.04
DM	3 (5.6)	1 (2)	>0.05

TPN: Total parenteral nutrition, UTI: Urinary tract infection,
PRM: Premature rupture of membranes, HT: Hypertension, DM: Diabetes mellitus

Discussion

Preterm infants face with the problems related to preterm delivery in addition to perinatal and postnatal risks. In studies comparing term infants and preterm infants, creatinine excretion in the first 24 hours was shown to be better in term infants and it was reported that increased creatinine in preterm infants was related to immature vessel structure (10,11).

Inadequate maturation in all systems in preterm infants usually leads to TPN in these infants. In this study in which we assumed that inadequate renal functions in preterm infants receiving TPN would deteriorate further, especially serum cystatin C, urinary β2M, GSTπ and NAG values were found to be significantly higher on the 30th day in the TPN group compared to the enteral feeding group and compared to the third day. This finding was found to be considerably significant in terms of showing the negative effects of TPN on renal function in preterm infants before oligo-anuria develops and serum creatinine values increase.

It was found that maturation of renal functions in preterm infants was slower compared to term infants and this was increased further with use of aminoglycosides (12). In the

Table 3. Biochemical variables of the patients on the third and 30th days

	Day	Enteral	TPN	p
BUN (mg/dL)	3	18.1±12.5	21.6±12	>0.05
	30	11.2±6.3	13.8±8	>0.05
Creatinine (mg/dL)	3	0.93±0.24	1.0±0.2	0.009
	30	0.55±0.21	0.5±0.1	>0.05
Total protein (g/dL)	3	4.56±0.44	4.5±0.6	>0.05
	30	5.04±0.45	4.8±0.6	>0.05
Albumin (g/dL)	3	3.18±0.32	3.1±0.4	>0.05
	30	3.44±0.28	3.2±0.4	0.001
AST (U/l)	3	37.5±14.3	42.6±16.2	>0.05
	30	25.0±8.1	92.0±114.5	<0.001
ALT (U/l)	3	11.4±7.9	12.5±8.1	>0.05
	30	11.5±3.9	47.0±64.9	<0.001
ALP (U/l)	3	226.8±65.4	224.2±63.6	>0.05
	30	309.0±94.7	471.6±180.5	<0.001
Sodium (mmol/l)	3	139.2±4.9	136.9±5	0.01
	30	137.9±2.7	137.2±3.1	>0.05
Potassium (mmol/l)	3	4.8±0.7	4.3±0.7	>0.05
	30	4.7±0.7	4.3±0.7	0.004
Calcium (mg/dL)	3	8.7±1.1	8.3±1.0	0.038
	30	9.7±0.8	9.5±0.8	>0.05
Phosphorus (mg/dL)	3	4.9±1.9	4.9±2.1	>0.05
	30	6.3±1.4	5.3±1.9	0.001

Table 4. Serum cystatin C and urinary β2M, GSTπ, NAG levels of the patients on the third and 30th days

	Gün	Enteral	TPB	p
Cystatin C (mg/L)	3 30	1.3±0.3 1.3±0.2	1.2±0.2 1.6±0.3	>0.05 <0.001
Beta 2 microglobulin (mg/L)	3 30	5.2±3.9 4.1±3.1	3.8±1.9 10.6±7.3	>0.05 <0.001
Glutathione-S-transferase π (ng/mL)	3 30	5.5±3.0 9.9±17.2	6.7±1.9 44.3±63.6	>0.05 <0.001
N-acetyle beta-D glucosaminidase (µg/L)	3 30	4.2±3.2 4.8±2.2	2.9±1.6 7.3±7.8	>0.05 <0.001

study in which Gibey et al. (13) compared distal tubular functions of term and preterm infants, Na uptake was found to be better in term infants compared to preterm infants and use of aminoglycosides was found to severely deteriorate tubular functions and disrupt Na absorption in preterm infants. When the patients in our study were evaluated in terms of use of aminoglycosides, no statistically significant difference was found between the TPN group and the enteral feeding group. We think that this finding is significant in that use of aminoglycoside which has a potential to deteriorate renal functions is not a variation to decrease the value of the study.

Low birth weight and gestational age are the most important risk factors for RDS. The other risk factors include male gender, cesarean delivery and multiple pregnancy (14). RDS is observed with a rate of 60-80% in preterm infants younger than 28 weeks or below, with a rate of 50% in infants with a gestational age of 28-32 weeks and with a rate of 15-30% in infants with a gestational age of 32-36 weeks (1,14). In infants in whom surfactant and mechanical ventilation are used because of RDS, the most severe early complications include air leaks, pneumoniae, central nervous system bleedings and sepsis (1). Because of these complications these patients need to receive TPN for a longer time. In our study, the rate of RDS was found to be 44.4% in the TPN group and 52% in the enteral feeding group and the difference was not statistically significant.

NAG which is a noninvasive test has a significant role in early diagnosis and follow-up of renal damage caused by toxins and other reasons. N-acetyle glucosamidase is found in the proximal tubules and is used to evaluate the function of this region (15). However, in parallel to renal pathologic changes, the amount of NAG in urine is increased in an earlier period compared to renal function tests which are used frequently (7). With this objective it is used reliably as an early marker in some conditions including hypertension, diabetes mellitus, proteinuria, drug-related nephrotoxicity and rejection after renal transplantation (16-19). In studies performed in preterm and term neonates, urinary NAG excretion has been reported to be one of the important markers to show renal tubular damage (20,21,22,23,24). We could find no study related to measurement of urinary NAG excretion in preterm infants receiving TPN in the literature. In our study, urinary NAG levels in preterm infants who received TPN and who were fed enterally were compared on the third and 30th days and no significant difference was found in urinary NAG values in the enteral feeding group. In the TPN group, urinary NAG values were found to be significantly higher on the 30th day compared to the third day. This finding suggested that urinary NAG levels could also be used to show the negative effects of TPN on the kidneys.

Cystatin C is a cystein proteinase inhibitor with a structure of non-glycolsyed polypeptide with a weight of 13 kDa containing 122 amino acids. It is produced at a constant speed in all nucleated cells. Cystatin C does not have certain rhythm during the day. It is considered to be a more sensitive variable in evaluating glomerular filtration rate because it has a constant production rate, it is filtrated freely from the glomerules and it is not affected by the body muscle mass in contrast to creatinine (25). Newman et al. (26) showed that cystatin C was a better variable compared to creatinine in determining small changes in GFR in a study they performed in 469 patients. In a study performed in 108 preterm infants in Turkey, it was stated that cystatin C might be an option to evaluate renal functions, but it was not evaluated if it had superiority compared to creatinine and it was emphasized that this was related to the low number of subjects (27). In our study, no statistically significant difference was found between serum cystatin C levels measured on the third and 30th days in the patients who were fed enterally. In the TPN group, serum cystatine C level was found to be higher on the 30th day and the difference was statistically significant. No study related to use of cystatin C as a marker of renal damage caused by TPN could be found in the literature. Our results showed that TPN might have a negative effect on the kidneys and glomerular damage can be determined using cystatin C in the early period when oligo-anuria has not developed and creatinine has not increased.

β2 microglobulin is a part of HLA class I molecule expressed on the surface of nucleated cells. It is found in the light chain of HLA class I molecule. β2M which is a low molecular weight protein freely passes into the glomerular filtrate and nearly one hundred percent of the filtrated protein is reabsorbed. Proximal tubulus cells constitute the main place of β2M catabolism. With these properties it is thought that β2M can reflect early proximal tubular damage. Perlamn et al.(28) evaluated the rates of complications in the urinary system, central nervous system, respiratory system, cardiovascular system and gastrointestinal system in a study and found that oliguria was related to increased serum creatinine level and urinary β2M levels. In the study performed by Fields et al. (29), increased β2M level was found to be a more sensitive marker compared to creatinine for rejection. In our study, urinary β2M levels on the 30th day were found to be higher in the TPN group compared to the enteral feeding group and the difference was statistically significant. Our results are

compatible with the results of the literature. Increased urinary β2M levels shows that TPN may have a negative effect on proximal tubular renal functions.

Glutathione-S-transferases constitute only 2% of the total protein in the cytoplasm. In case of increased permeability of cell membrane or cell damage, their serum levels in the extracellular space are increased. Therefore, observation of glutathione-S-transferases is evaluated to be an indicator of renal disease or damage (30,31). In a study performed in 56 patients with glomerular disease and proteinuria, increased urinary GSTπ was found to be compatible with creatinine clearance and the highest values were found in pateints with renal failure. In this study, it was reported that GSTπ might be useful in indicating tubular cell damage caused by proteinuria (32). In our study, urinary GSTπ values were not found to be statistically significantly different on the third and 30th days in the patients who were fed enterally, but found to be significantly higher on the 30th day in the TPN group. Although few studies conducted in preterm infants are found in the literature, the fact that our results were similar to the results of other studies performed in other patient groups showed that the effect of TPN on distal tubular functions could be shown by measuring urinary GSTπ in the early period.

There are no studies evaluating TPN in preterm infants and all of these variables in association in similar patient groups in the literature. This study is important in that it is the first study showing that TPN may have negative effects on glomerular and tubular functions in the kidney and this can be determined in the early period with serum cystatin C, urinary β2 microglobulin, GSTπ and N-acetyle β-D glucosamidase. However, we believe that our results should be supported by studies including larger series and more "homogeneous" patient groups, since we could not achieve similarity especially in terms of gestational week between the groups in our study.

Conflict of interest: None declared.

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