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The association between urinary BPA levels and medical equipment among pediatric intensive care patients

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ABSTRACT

We aim to evaluate urinary total BPA (tBPA) levels and association with medical devices used on patients in pediatric intensive care units. This cross-sectional descriptive study included 117 critically ill children. Urinary tBPA levels were determined using high-performance liquid chromatography. General estimating equations with repeated measures analyzed the effect of interventions and devices on urinary BPA levels. A total of 292 urine samples taken from 117 child intensive care patients were studied. When age, sex, and body mass index-for age z-scores were controlled, cases having endotracheal intubation showed higher urinary tBPA levels ($p = 0.003$) and hemodialyzed patients had considerably higher urinary tBPA levels ($p = 0.004$). When confounding factors were controlled, cases using both multiple iv treatment and more than four medical devices showed higher urinary tBPA levels than their counterparts ($p = 0.007$ and $p = 0.028$, respectively). The use of certain medical devices and interventions could increase BPA exposure in pediatric intensive care patients.

1. Introduction

Bisphenol A [2, 2-bis (4-hydroxyphenyl) propane, BPA] is an industrial chemical consisting of two phenol molecules and polycarbonates. Polycarbonates are widely used in plastics (Zoeller et al., 2005). Exposure to BPA usually occurs through the ingestion of food and drinks resulting from BPA usage in food packaging, orally during dental treatment due to the use of materials containing resin, directly from skin contact with thermal papers or systematically through any materials used in parenteral treatment (Abraham and Chakraborty, 2020). Numerous research studies in the last few years have shown the potential negative effects of BPA on human health including the whole endocrine, nervous and metabolic systems (Mansouri et al., 2019; Tomza-Marciniak et al., 2018). It may lead to diabetes, obesity, allergic reactions, asthma, autoimmune diseases and cancer as well as many other disturbances including behavioral and developmental problems in children (Abraham and Chakraborty, 2020; den Braver-Sewradj et al., 2020; Freire et al., 2020; Howard, 2018; Mustieles and Fernández, 2020; Tomza-Marciniak et al., 2018; Zhang et al., 2020).

Providing information about the negative effects of BPA has led to the manufacture of BPA-free products for babies (Fox et al., 2011). However, despite the research being done today, the manufacture of BPA-free medical supplies has not yet been considered in many countries (Testai et al., 2016). BPA exposure of intensive care unit (ICU) patients can be higher than expected because of the use of medical materials such as plastic infusion bags, infusion sets, intravenous catheters, hemodialysis equipment, urinary catheter, drainage tubes, ventilation equipment, humidifiers, nasogastric tubes and feeding equipment which are used for intravenous treatments, transfusions, hemodialysis and mechanical ventilation (Iribarne-Durán et al., 2019; Testai et al., 2016). It should be remembered that these patients all have critical diseases and the excretion of toxic substances in their bodies is more difficult due to decreased perfusions of patients and also underdeveloped metabolism of children. There are some studies conducted in adult and neonatal ICUs (Calafat et al., 2009; Duty et al., 2013; Huygh et al., 2015). The first study to focus on BPA exposure among patients in neonatal ICU in 2009 reported that premature babies exposed to intensive interventions had a high BPA urine concentration in comparison with the general

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population (Calafat et al., 2009). In addition, a study in neonatal ICU collected 104 urine samples from 55 patients and determined higher urine BPA levels in babies that use four or more medical devices when compared to those that use less than four (Duty et al., 2013). Increased exposure due to longer treatment duration or multiple equipment usage may augment the risk of toxicity in patients. However, neither of these two studies stated the medical interventions separately. Therefore, it was impossible to understand which medical intervention had increased BPA levels the most. There is no prospective study evaluating changes in exposure status during follow-up period in pediatric ICU (PICU). This longitudinal research aims to evaluate the urinary total BPA (tBPA) levels of pediatric patients in ICU and any association with medical devices used during treatment. With this research, procedures which have high exposure rates can be defined and mitigation initiatives can be planned.

2. Materials and method

2.1. Study design

A cross-sectional descriptive study was conducted in Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital. This study received approval from the Local Clinical Research Ethical Committee.

PICU patients were enrolled in this study after a written form of consent for voluntary participation had been obtained from the parent of each child. Being between 1 month and 18 years of age, having used at least one medical material containing plastic for at least 48 h, calculations showing that the patient would not be discharged from the intensive care unit for one week and patients whose 'informed consent' had been approved were included in the study. Anuric patients were excluded from the study.

It was planned to take 3 urine samples from each participant: on the first day of Intensive Care, 7 days later and finally 30 days later (or at the time of discharge). For each patient, all the materials used, along with the procedures applied (such as peripheral or central infusion bags, total parenteral nutrition (TPN), nasogastric (NG) tube or permanent NG tube, percutaneous gastrostomy (PEG) tube, endotracheal intubation tube, tracheostomy cannula, chest drain tube system, extraventricular drainage (EVD) set, surgical drain, ventilation equipment, nasal cannula, oxygen mask, hemodialysis, continuous venovenous hemodiafiltration (CVVHDF), plasma exchange, central venous catheter (CVC), hemodialysis catheter (HDC), inhalation treatment, transfusion of blood products, etc.) and duration of procedures were recorded on the patient's form.

Patient urine samples were obtained in glass bottles. Urine samples measuring approximately 2 mL were taken into BPA-free glass tubes and then stored at -80 degrees celsius until they were to be studied. After all the samples had been collected they were sent to and studied in the Department of Toxicology, Faculty of Pharmacy, Hacettepe University.

The height and weight of each patient were recorded in the patient file. The body mass index (BMI) was calculated by weight (kg)/height $(m)^2$ formula. BMI for age z-scores (BAZ) and height for age z-scores (HAZ) were calculated using the World Health Organization references (WHO Anthro., 2011). Hemoglobin, white blood cell (WBC), platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine values of the same date as the urine had been taken were recorded in the patient files. When the test results were not on the same date, we used the records from the previous day or the following day.

Patients were divided into two groups according to 'acute exposure' to medical vehicle usage (for the first time in intensive care or not having to use medical devices on a continuous basis) or 'chronic exposure' (patient dependent on a continuous medical device such as PEG tube, permanent nasogastric tube, tracheostomy cannula). Those classified as 'acute exposure' were then divided into three groups as mild exposure (patients with two or fewer medical devices), medium exposure (patients with three or four medical devices) and severe exposure (patients with more than four medical devices). This study received approval from the Clinical Research Ethical Committee of our institution (Number: GO 18/570).

2.2. BPA measurement

2.2.1. Purification of glass materials from plastic

Throughout all the experiments, only glass material was used to avoid contamination from plastic materials. All the glass tubes were deplasticized prior to the study by being heated at 400 °C for 4 h. Other glass materials were purified from plastic remains by being washed in n-hexane: tetrahydrofuran (1:1, v/v) for 4 h and dried in an incubator.

2.2.2. Extraction

50 µl 100 ng/mL (ppb) BPA were added to 500 µl urine samples for tBPA analysis (conjugated plus free). Then, 30 µl 2.0 M sodium acetate buffer solution (pH 5.0) and 10 µl glucuronidase/arylsulfatase (*Helix pomatia*) were added to the mixture and mixed. The new mixture was incubated in a 37 °C water bath for 3 h. Following that, the mixture was extracted with 5 mL acetate and centrifuged in 3500 rpm for 5 min. 3 mL of the supernatant was transferred to another glass tube and evaporated under Nitrogen gas until there was a residue. The residue was then stored at −20 °C until it could be analyzed.

2.2.3. Chromatographic system

The determination of BPA was carried out with a method consisting of BPA extraction from urine with a sodium acetate buffer solution and ethyl acetate, followed by evaporation under nitrogen gas and solution of the residue in the mobile phase and quantity calculation using the HPLC technique. The analysis was done using HPLC (Hewlett Packard Agilent 1200 Series, Vienna, Austria). In the HPLC system, fluorescence detector (excitation $\lambda = 230$ nm, excitation $\lambda = 315$ nm), Spherisorb C18 ODS2 colon (particle size 5 µm, 25 cm, 4.6 mm i.d.) (Waters, Milford, MA) is used. The injection volume is 100 µl. The colon heat is 25 °C.

2.2.4. Application of the method

The samples stored at −20 °C after extraction were solved in 300 µl 60 % acetonitrile. Each standard and sample was injected to HPLC as 100 µl. The mobile phase consisted of acetonitrile and 2.5 % (v/v, in water) tetrahydrofuran and its flow rate was 0.4 mL/min. Gradient elution was applied as 60:40 to 5:95.

2.2.5. Properties of the BPA method

The retention time for BPA was determined to be 18.1–18.7 min. BPA standards were used in the calculations and these calculations were made using the height under the curve. As a result of 10 different analyses in recycling studies, recycling for BPA was determined to be 95.27 ± 1.23 % (mean + standard deviation, SD). The difference in the day (in CV) was determined to be 2.76 ± 0.24 %. The difference between the days was determined to be 2.63 ± 1.23 %. LOD was 1 ng/mL, and LOQ was 2.5 ng/mL.

2.2.6. Determination of the urine creatinine

To normalize the results, the urine creatinine levels were also measured. Urine creatinine levels were determined by making modifications to the previous method with HPLC (Jen et al., 2002). A 15 mM potassium dihydrogen phosphate buffer solution containing 2.5 % methanol (pH 7) was used as the mobile phase. The analyses were made in C18 colon with a UV detector at 235 nm wavelength. Creatinine standard solutions were prepared. The urine samples were diluted with deionized water at a 1/10 ratio. Analyses were made in chromatographic conditions as described in detail above. The creatinine levels of the samples were calculated as ng/mL, also considering the peak areas of the standard and the samples. The results were multiplied by 10 since the samples had been previously diluted.

2.3. Data analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was evaluated with the Shapiro-Wilk test, kurtosis, skewness and histograms. The numerical variables that show normal distribution were given as mean and standard deviations (SD) and the ratios of the categorical variables were evaluated with the chi-square test.

Levels below the limit of detection (LOD) were replaced with values of LOD/$\sqrt{2}$.

Interactions between the urinary tBPA levels and childhood parameters during follow period were analyzed with repeated generalized estimating equations (scale response: gama with log-link and correlation matrix dimension = 3). After controlling confounding factors (age, sex, and BAZ), the data was re-analyzed by repeated generalized estimating equations. Pairwise comparisons in groups having more than two subtypes were performed with "least significant difference" test. Estimated marginal mean with standard error (SE) were given.

A value of $P < 0.05$ was accepted as meaningful.

3. Results

In total 117 patients in our PICU who met the inclusion criteria were included in the study. The female to male ratio was 50/67, and the mean age was 6.0 years. Table 1 shows the distribution of diagnoses and demographics for patients.

A total of 292 urine samples from 117 PICU patients were collected. Overall 91.5 % of the 1st samples, 95.7 % of the 2nd samples and 98.3 % of the 3rd samples had detectable tBPA levels.

After classifying according to the duration of exposure to a particular medical device, the mean (±SE) tBPA levels were determined as 118.2 ± 19.8 μg/g-creatinine in acute exposure and 124.9 ± 39.4 μg/g-creatinine in chronic exposure (p = 0.880). In acute exposure, the tBPA levels increased gradually according to the severity of exposure. However, this increase was also statistically not significant (p = 0.329, Table 2).

In patients with endotracheal intubation, the tBPA levels were significantly higher than the tBPA levels of patients without intubation (166.0 ± 30.9, 68.6 ± 11.9 μg/g-creatinine, respectively; p = 0.003). The urine samples of patients with intubation for more than 3 days had significantly higher tBPA levels in comparison to the tBPA levels of patients with intubation for 3 days or less (245.5 ± 63.3, 101.7 ± 29.0 μg/g-creatinine, respectively; p < 0.001). This statistical significance also continued after adjustment according to the child's age, sex and BAZ (p < 0.001). Whether or not the patient had received a tracheostomy, NIV cannula, O_2 cannula, or O_2 mask did not influence the tBPA levels (Table 3).

Taking digestion medical supplies into consideration, there was no interaction between the existence of a NG or PEG tube and urine tBPA levels. However, tBPA levels were significantly lower in patients with a permanent NG than counterparts (38.8 ± 12.9, 123.4 ± 18.5 μg/g-creatinine, respectively; p < 0.001, Table 4). The association was present when adjusted for age, gender, body mass index for age z-scores.

When catheter type was evaluated, urine tBPA levels were not associated with CVC whereas HDC significantly increased tBPA levels (p = 0.034). Having been hemodialyzed also significantly increased urine tBPA levels, (p = 0.026) and when adjusted according to age, sex, and BAZ, this significance was clearly evident (p = 0.004, Table 5).

When drainage systems were evaluated, mean urinary tBPA levels were significantly lower in the presence of anyone of EVD, chest tube drainage system or surgical drain compared to the usage of no drains, (44.3 ± 13.0, 134.5 ± 20.7 μg/g-creatinine, respectively; p < 0.001, Table 6). When adjusted according to age, gender and BAZ, if there was no drain, mean tBPA levels were still higher compared to when there was a drainage system, (129.5 ± 18.8, 32.6 ± 20.6 μg/g-creatinine, respectively; p < 0.001, Table 6).

As a whole, cases receiving multiple intravenous (iv) treatments had higher urinary tBPA levels in comparison to those not receiving it and tBPA levels were detected to be higher in cases using four or more medical devices when compared to those using less than four devices (177.3 ± 35.2, 73.6 ± 12.7 μg/g-creatinine, respectively; p = 0.007 and 157.7 ± 31.7, 86.7 ± 12.1 μg/g-creatinine respectively; p = 0.028, Table 6).

Furthermore, tBPA levels were similar in cases having low levels and normal limits of blood parameters including hemoglobin, WBC, platelet, AST, ALT and creatinine values.

Table 1
Baseline Clinical and Demographic Features.

Variables	Case-based (n = 117)	Urine sample based (n = 292)
Age, years, n(%)		
0–1	21 (17.9)	51 (17.5)
>1–5	39 (33.3)	95 (32.5)
>5–10	27 (23.1)	69 (23.6)
>10	30 (25.6)	77 (26.4)
Sex		
Female	50 (42.7)	126 (43.2)
Male	67 (57.3)	166 (56.8)
Height z-score, mean ± SD	−0.86 ± 1.68	
BMI z-score, mean ± SD	−0.39 ± 1.55	
Underlying Diseases of patients, n (%)		
Neurological Diseases	21 (17.9)	54 (18.5)
Neurometabolic Diseases	16 (13.7)	44 (15.1)
Congenital Anomaly and Syndromes	12 (10.3)	30 (10.3)
Immune Deficiencies	6 (5.1)	14 (4.8)
Other Diseases	3 (2.6)	9 (3.1)
No Underlying Diseases	59 (50.4)	141 (48.3)
Associated disease on Admission, n (%)		
Infectious Diseases	57 (48.7)	143 (49.0)
Traumas	26 (22.2)	64 (21.9)
Acute Neurological Disease	13 (11.1)	36 (12.3)
Hematological and Oncological Diseases	9 (7.7)	23 (7.9)
Poisoning	4 (3.4)	9 (3.1)
Other Diseases	8 (6.8)	17 (5.8)
Blood parameters, median (Q1-Q3)		
Hemoglobin, g/dL		10.8 (9.5–11.9)
WBC, 10^3/μL		10.6 (8.0–15.1)
Platelet, 10^3/μL		288.0 (188.3–421.8)
Creatinine, mg/dL		0.43 (0.34–0.57)
AST, U/L		37.0 (26.0–58.0)
ALT, U/L		24.0 (14.0–46.8)
t-BPA		
μg/g-creatinine, Median (Q1-Q3)		
1st sample, n = 117	29.5 (5.6–78.3)[a]	
2nd sample, n = 117	41.1 (9.6–141.4)[b]	
3rd sample, n=58	104.8 (47.5–241.6)[c]	

SD: Standard deviation, BMI: Body mass index, WBC: White blood cell, AST: Aspartat aminotransferase, ALT: Alanine aminotransferase.
Q1-Q3: the first and third quartiles.
a, b and c: Means followed by different letters are significantly different from others (P<0.05).

4. Discussion

In the present study, the median urinary BPA level which was 29.5 μg/g-creatinine for the 1st sample of PICU patients from Ankara in Turkey were similar to the levels among hospitalized premature infants (n = 42, median 28.6 μg/L; range = 1.6–946 μg/L) from Massachusetts in USA, whereas, higher than the level (median = 3.7 μg/L; 95th percentile = 16.0 μg/L) among children 6–11 years of age who were examined as part of the NHANES 2003–2004 (Calafat et al., 2009) and samples from healthy children (median = 1.97 μg/L; 95p = 13.14 μg/L) collected in 2011–2012 from six European countries (Huang et al.,

Table 2
Mean urinary total BPA levels (μg/g-creatinine) according to patients' characteristics.

	n (292)	tBPA* (mean ± SE)	p	tBPA** (mean ± SE)	p
Suspected exposure duration					
Acute	217	118.2 ± 19.8	0.880	113.9 ± 20.8	0.917
Chronic	75	124.9 ± 39.4		118.7 ± 37.9	
Suspected exposure duration and severity					
Acute mild exposure	76	82.1 ± 20.1	0.366	76.1 ± 21.8	0.329
Acute medium exposure	76	131.1 ± 41.9		127.3 ± 40.8	
Acute severe exposure	65	145.5 ± 36.5		145.4 ± 38.3	
Chronic exposure	75	124.9 ± 39.4		118.2 ± 37.9	
Children's age					
0–1 age	51	87.2 ± 22.0	0.208	89.7 ± 22.5	0.200
> 1–5 years old	95	160.9 ± 33.6		155.3 ± 33.1	
> 5–10 years old	69	131.4 ± 47.0		128.2 ± 44.3	
10 years	77	81.0 ± 26.3		75.8 ± 27.7	
Children's gender					
Male	166	124.3 ± 25.6	0.774	114.5 ± 21.5	0.898
Female	126	114.2 ± 24.0		110.0 ± 24.8	

tBPA: total Bisphenol A.
* Repeated generalized estimating equations evaluated the effect of the selected predictor on the urinary tBPA levels.
** Repeated generalized estimating equations determined the effect of the selected predictor on the urinary tBPA levels after controling for age, gender, body mass index for age z-scores.

2018). Similarly, urinary BPA was detected in 76.8 % of children from < limit of quantification to 18.36 μg/g-creatinine in preschool children taken in 2015–2016 from Ankara in Turkey (Çok et al., 2020). The present study levels were also extremely high from the previous reports in children having idiopathic central precocious puberty (median BPA = 8.34, range = 0.84–67.35 μg/g creatinine) (Durmaz et al., 2014). However, mean BPA levels was 27.71 ± 15.53 [range 5.28–81.11] μg/g creatinine in the T1DM group from Ankara in Turkey (İnce et al., 2018). Moreover, the median urinary BPA level in the present study was found to be 41.1 μg/g-creatinine for the 2nd sample (Day 7) and 104.8 for the 3rd sample (Day 30) in PICU cases. Previous studies had some differences in age group (newborn, preschool children, school children) and unit of BPA being creatinine adjusted or not. However, all of these conditions could not explain the extreme levels in children having different medical equipments in the PICU.

In the present study, acute or chronic exposure to medical devices did not create any difference while the usage of four or more medical devices did. Similarly, a study in NICU reported premature cases using 4 or more medical devices had nearly three times more tBPA levels in compared to 0–3 devices (36.6 vs. 13.9 mg/L; p = 0.02) and remained 1.6 times higher after adjusting confounding factors (Duty et al., 2013). Moreover, those patients who had received multiple intravenous treatments had significantly higher tBPA levels in the present study.

In the present study, endotracheal intubation had a significant distinction and that in comparison to patients that never have intubation, intubated patients have significantly increased urinary BPA levels. In addition duration of endotracheal intubation was associated with the levels.

High BPA content reported in endotracheal tubes in the previous study supports the results (Iribarne-Durán et al., 2019). No association were detected between tracheostomy cannula usage and urinary tBPA levels. These results may be caused by decreased BPA leakage in tracheostomy cannulas due to the usage of high-quality materials that increase durability in such supplies. In the present study BPA levels were not associated with nasal cannula and O_2 mask. However, a study in NICU reported higher total urinary BPA in cases having nasal cannula than others (Duty et al., 2013). The differences may be partially due to age groups, exposed levels and used equipment.

The present study revealed high urinary BPA levels in cases having hemodialysis. Additionally, in patients using a hemodialysis catheter, urine BPA levels were significantly higher than in patients with a central venous normal catheter. We think that this difference is also caused by exposure to hemodialysis. In a study conducted in 2019, serum BPA levels and three BPA analogs were found to be significantly higher in adult patients with hemodialysis than in patients with peritoneal dialysis. They also mentioned that hemodialysis filters can contribute to bisphenol burden in patients on hemodialysis (Shen et al., 2019). Murakami et al. discoursed that serum BPA levels are related to the dialyzer used among adult patients with chronic renal failure. They also found that serum BPA levels increased as kidney function deteriorated (Murakami et al., 2007). Nevertheless, in our study, we did not find any relationship between serum creatinine levels and urine BPA levels.

Table 3
Mean urinary total BPA levels (μg/g-creatinine) according to used respiratory device type.

Medical device type	n	tBPA* (mean ± SE)	p	tBPA** (mean ± SE)	p	tBPA*** (mean ± SE)	p
Endotracheal intubation during time							
No	138	68.6 ± 11.9	<0.001	62.7 ± 14.2[a]	<0.001		
≤3 days	48	101.7 ± 29.0		93.9 ± 25.8[a]			
>3 days	46	245.5 ± 63.3		245.7 ± 59.6[b]			
Removed	60	156.4 ± 29.5		152.5 ± 28.5[b]			
Endotracheal intubation status							
No	138	68.6 ± 11.9	0.003	61.8 ± 14.6	0.003	54.1 ± 27.3	0.001
Yes/removed	154	166.0 ± 30.9		162.8 ± 28.0		152.7 ± 29.4	
Tracheostomy status							
No	256	124.7 ± 20.0	0.241	72.9 ± 31.9	0.188	115.3 ± 16.7	0.515
Yes	36	86.5 ± 25.7		120.9 ± 18.5		91.4 ± 39.0	
Non-invaziv cannula status							
No	203	124.7 ± 22.6	0.590	117.2 ± 20.5	0.832	102.3 ± 19.9	0.941
Yes	89	109.0 ± 21.7		110.9 ± 24.0		104.4 ± 34.1	
O_2 cannula or O_2 mask status							
No	236	119.3 ± 20.8	0.907	116.6 ± 19.4	0.794	103.8 ± 18.9	0.977
Yes	56	122.8 ± 23.6		108.7 ± 23.6		103.0 ± 34.8	

tBPA: total Bisphenol A; SE: standard error.
a and b; Means followed by different letters are significantly different from others (P < 0.05).
* Repeated generalized estimating equations evaluated the association with the selected predictor and the urinary tBPA levels.
** Repeated generalized estimating equations evaluated the association with the selected predictor and the urinary tBPA levels after controling for age, gender, body mass index for age z-scores.
*** Repeated generalized estimating equations evaluated the associations with all selected respiratory devices and the urinary tBPA levels after controling for age, gender and body mass index for age z-scores.

Table 4
Mean urinary total BPA levels (μg/g-creatinine) according to used gastrointestinal device type, and urinary catheter.

Medical device type	n	tBPA* (mean ± SE)	p	tBPA** (mean ± SE)	p	tBPA*** (mean ± SE)	p
Nasogastric tube							
No	116	104.0 ± 21.0	0.420	97.2 ± 24.4	0.373	62.1 ± 19.0	0.600
Yes	176	130.5 ± 25.8		127.4 ± 22.8		82.3 ± 40.6	
Permanent nasogastric tube							
No	280	123.4 ± 18.5	<0.001	119.6 ± 17.5	<0.001	113.7 ± 20.1	0.037
Yes	12	38.8 ± 12.9		24.2 ± 19.4		30.6 ± 40.7	
Percutanoeus gastrostomy tube							
No	270	120.4 ± 19.0	0.892	116.3 ± 17.3	0.682	68.2 ± 41.9	0.835
Yes	22	115.1 ± 34.2		102.1 ± 33.1		76.1 ± 15.1	

tBPA: total Bisphenol A; SE: standard error.
* Repeated generalized estimating equations evaluated the association with the selected predictor and the urinary tBPA levels.
** Repeated generalized estimating equations evaluated the association with the selected predictor and the urinary tBPA levels after controling for age, gender, body mass index for age z-scores.
*** Repeated generalized estimating equations evaluated the associations with all selected gastrointestinal devices and the urinary tBPA levels after controling for age, gender and body mass index for age z-scores.

Table 5
Mean urinary total BPA levels (μg/g-creatinine) according to used catheter type and replacement treatments.

Medical device type	n	tBPA* (mean ± SD)	p	tBPA** (mean ± SD)	p
Central venous catheter					
No	139	104.3 ± 23.5	0.318	95.0 ± 18.5	0.163
Yes	153	134.2 ± 23.1		133.9 ± 23.7	
Hemodialysis catheter					
No	268	109.6 ± 17.8	0.089	102.0 ± 16.3	0.034
Yes	24	236.0 ± 73.0		252.4 ± 70.7	
Hemodialysis					
No	284	115.9 ± 17.8	0.026	110.8 ± 17.1[a]	0.004
Yes	5	214.5 ± 129.3		225.8 ± 113.2[b]	
Finished	3	342.3 ± 92.9		335.1 ± 72.7[b]	
Hemodialysis procedure					
No	284	115.9 ± 17.8	0.208	110.8 ± 17.1	0.119
Yes/Finished	8	262.5 ± 115.7		267.2 ± 97.8	
Plasma exchange					
No	284	119.9 ± 18.3	0.927	114.6 ± 17.1	0.561
Yes/finished	8	122.9 ± 28.2		136.6 ± 33.8	
Continuous veno-venous hemodiafiltration					
No	287	113.7 ± 17.3	0.101	106.5 ± 15.3	0.060
Yes	5	480.8 ± 223.9		522.2 ± 222.4	

tBPA: total Bisphenol A; SE: standard error.
a and b; Means followed by different letters are significantly different from others ($P < 0.05$).
* Repeated generalized estimating equations evaluated the effect of the selected predictor on the urinary tBPA levels.
** Repeated generalized estimating equations determined the effect of the selected predictor on the urinary tBPA levels after controling for age, gender, body mass index for age z-scores.

Huygh et al. have analyzed 102 urine samples in 35 adult intensive care patients according to their BPA exposure (Huygh et al., 2015). They concluded that adult intensive care patients are also exposed to BPA and that patients with continuous venous hemofiltration and extracorporeal membrane oxygenation have significantly higher urine BPA levels (Huygh et al., 2015). Even though the urine BPA levels of our CVVHDF patients were higher after the interventions than before, this difference was not statistically significant. On the other hand, it is not possible to reach a clear conclusion about this issue since, in our study, only a limited number of cases had CVVHDF.

Table 6
Mean urinary BPA levels (μg/g-creatinine) according to drain type and other treatment procedures.

	n (292)	tBPA* (mean ± SD)	p	tBPA** (mean ± SD)	p
Extra-ventriculer drainage					
No	288	121.4 ± 18.1	<0.001	116.5 ± 16.8	0.023
Yes	4	16.9 ± 9.6		10.0 ± 44.5	
Chest drain					
No	271	126.9 ± 19.0	<0.001	121.4 ± 17.4	<0.001
Yes	21	30.2 ± 9.2		18.4 ± 24.3	
Surgical drain					
No	270	124.6 ± 19.1	0.051	120.4 ± 17.7	0.073
Yes	22	62.6 ± 25.4		50.4 ± 33.5	
Drains					
No	245	134.5 ± 20.7	<0.001	129.5 ± 18.8	<0.001
Yes	47	44.3 ± 13.0		32.6 ± 20.6	
Drain type					
No	245	134.5 ± 20.7	<0.001	129.4 ± 18.8b	0.001
Extra-ventriculer drainage	4	16.9 ± 9.6		5.8 ± 47.4a	
Surgical drain	22	62.6 ± 25.4		50.3 ± 32.9a	
Chest drain	21	30.2 ± 9.2		17.9 ± 24.3a	
Urinary catheter					
No	76	93.2 ± 22.8	0.162	76.8 ± 22.8	0.095
Yes	216	130.8 ± 23.1		129.2 ± 21.4	
Other procedures					
Inhaler treatment					
No	170	140.9 ± 28.2	0.119	134.9 ± 26.3	0.122
Yes	122	90.8 ± 15.3		88.6 ± 15.9	
Total parenteral nutrition					
No	280	122.3 ± 18.5	0.077	116.1 ± 17.0	0.538
Yes	12	65.2 ± 26.8		93.9 ± 34.0	
Blood product transfusion					
No	215	106.7 ± 18.0	0.251	103.0 ± 17.2	0.252
Yes	77	157.0 ± 41.3		153.0 ± 40.8	
Multiple intravenous treatment					
No	169	77.4 ± 11.2	0.010	73.6 ± 12.7	0.007
Yes	123	178.4 ± 37.7		177.3 ± 35.2	
≥4 Use of medical device					
No	170	91.2 ± 13.2	0.031	86.7 ± 12.1	0.028
Yes	122	160.2 ± 32.9		157.7 ± 31.7	

tBPA: total Bisphenol A; SE: standard error.
a and b; Means followed by different letters are significantly different from others ($P < 0.05$).
* Repeated generalized estimating equations evaluated the effect of the selected predictor on the urinary tBPA levels.
** Repeated generalized estimating equations determined the effect of the selected predictor on the urinary tBPA levels after controling for age, gender, body mass index for age z-scores.

When we evaluated the drainage systems separately and together, the presence of EVD, chest tube drainage and surgical drainage systems showed lower mean tBPA levels than counterparts. There is no published study about this topic. As a hypothesis, while providing the outflow of secretions and purulent material, it can also support the removal of local contaminants from the body. In addition, we can also state that these

devices do not increase tBPA levels.

Cases having permanent NG usage had lower urine tBPA levels than cases without permanent NG. Overall, 5 cases had permanent NG and 12 samples were obtained from them. Two cases had neurometabolic diseases and three congenital anomaly. Four had tracheostomy and endotracheal intubation was applied to the other one at PICU. One had VP shunt due to hydrocephaly and chest drain. Due to limited number of cases additional studies are needed to investigate this results.

4.1. Strengths and limitations

The present study enrolled 117 cases having different medical equipment and procedures. During follow-up period, equipment, procedures and treatment types were changed. There were statements for the absence of BPA in only two tracheostomy cannulas. Of them, one case, 5 years of age had medullablastoma and had tracheostomy cannula, permanent nasogastric tube and some intravenous treatments; BPA levels were 5.0, 5.9 and 9.1 μg/g-creatinine during follow up period. Other case, 10-year-old, had status epilepticus and had tracheostomy cannula and some intravenous treatments; his urinary BPA levels were 33.7 and 2.1 μg/g-creatinine during follow up period. We could not examine an association between the BPA presence in devices and urinary BPA levels due to the absence of statement in user's manuals. With the results of the study, BPA content of selected devices which showed high urinary levels will be evaluated in further studies. Of all, 292 (2–3 per case) urine samples were taken and the used procedures were noted at each sampling time. Generalized estimating equations were applied to analyze the changes in follow-up period and among procedures. By this way, the associations between procedures and BPA can easily investigated. Also, BPA levels were adjusted with urine creatinine. As a limitation, cases had more than one equipment during follow up period and no samples were obtained after discharge. Further studies are necessary to evaluate the status after discharge from hospital.

5. Conclusions

These results suggest that medical devices in PICU were an important source for BPA exposure. In children with critical conditions that require several medical tools containing PVC for treatment, the number of medical devices used and the intensity of the treatment increases BPA exposure especially in need of intensive treatment. This exposure is especially prominent in acute cases that require endotracheal intubation and hemodialysis. It is important for the health of future generations that necessary precautions are taken for manufacturing all devices used in pediatric intensive care units to ensure that they are as BPA-free as possible.

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Authors' contributions

SSY and GA contributed to the conception or design of the work. GA and SE contributed to the acquisition of data. AY, AB, BK and PE performed laboratory analysis. SSY contributed to the statistical analysis and interpretation of data for the work. GA prepared the draft of the manuscript. SSY and GA gave the final manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Availability of data and materials

For access to the files, please send an e-mail request to siyalcin@hacettepe.edu.tr.

Ethical approval

Ethics Board of Non-Interventional Clinical Research from Hacettepe University approved the protocol. This study is doctorate thesis of Ganime Ayar.

Declaration of Competing Interest

The authors declare no conflict of interest.

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