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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The effect of preoperative balloon atrial septostomy and intraoperative parameters on neurodevelopmental scoring in neonates operated for transposition of the great artery

Büyük arter transpozisyonu nedeniyle ameliyat edilen yenidoğanlarda ameliyat öncesi balon atriyal septostominin ve intraoperatif parametrelerin nörogelişimsel skorlama üzerine etkisi

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ABSTRACT

Background: The aim of this study was to investigate the effect of preoperative balloon atrial septostomy and intraoperative parameters on neurodevelopmental outcomes in neonates operated for transposition of the great arteries.

Methods: Between February 2018 and March 2022, a total of 60 patients (49 male, 11 female; mean age, 23.5±8.8 days; range, 2 to 106 days) who were operated with a diagnosis of simple transposition of the great arteries and discharged uneventfully were included. Preoperative balloon atrial septostomy was performed in 33 patients (BAS+ group), while 27 patients (BAS– group) did not undergo the procedure. Finally, 13 patients from the septostomy group and 12 patients from the non-septostomy group were available for follow-up. Neurodevelopment in infants was assessed using the 3rd edition of the Bayley Scales of Infant and Toddler Development (Bayley-III) scoring.

Results: The mean cognitive, language, and motor composite scores were 85.00±11.73, 89.62±12.29, and 83.38±14.83 in the BAS+ group and 94.58±18.40, 99.83±15.71, and 90.00±18.73 in the BAS- group, respectively (p=0.131, p=0.123, and p=0.689, respectively). Ballon atrial septostomy was the only factor that caused a decrease in all composite scores according to Bayley-III scoring, although not statistically significant. There was a significant negative correlation between C-reactive protein and all composite scores. There was also a significant negative correlation between cardiopulmonary bypass time, cross-clamping time, mean plasma lactate levels (mmol/L) on postoperative Days 2-5, postoperative creatinine, and motor composite scores. There was a significant positive correlation between growth weight and head circumference and all three CSs.

Conclusion: Ballon atrial septostomy may adversely affect the neurodevelopmental process in neonates. We believe that close monitoring of postoperative blood values such as lactate, C-reactive protein and creatinine, and avoiding hypoxemia and keeping them at optimal levels are crucial. Good weight gain can also contribute to the neurodevelopment of patients.

Keywords: Balloon atrial septostomy, Bayley-III scoring system, neurodevelopmental outcomes, transposition of great arteries.

ÖZ

Amaç: Bu çalışmada, büyük arter transpozisyonu nedeniyle ameliyat edilen yenidoğanlarda ameliyat öncesi balon atriyal septostomi ve intraoperatif parametrelerin nörogelişimsel sonuçlar üzerindeki etkisi araştırıldı.

Çalışma planı: Şubat 2018 - Mart 2022 tarihleri arasında, basit büyük arter transpozisyonu tanısı ile ameliyat edilen ve sorunsuz bir şekilde taburcu edilen toplam 60 hasta (49 erkek, 11 kadın; ortalama yaş: 23.5±8.8 gün; dağılım, 2-106 gün) çalışmaya dahil edildi. Ameliyat öncesi balon atriyal septostomi 33 hastaya (BAS+ grubu) uygulanırken, 27 hastaya (BAS– grubu) bu işlem uygulanmadı. Son olarak, septostomi grubundan 13 hasta ve septostomi olmayan gruptan 12 hasta takip için mevcut idi. Bebeklerde nörogelişim, Bayley Bebek ve Küçük Çocuklar için Gelişim Ölçeği'nin 3. baskısı (Bayley-III) kullanılarak değerlendirildi.

Bulgular: BAS+ grubunda ortalama bilişsel, dil ve motor bileşik skorları sırasıyla 85.00±11.73, 89.62±12.29 ve 83.38±14.83, BAS– grubunda ise 94.58±18.40, 99.83±15.71 ve 90.00±18.73 idi (sırasıyla p=0.131, p=0.123 ve p=0.689). Bayley-III skorlamasına göre, istatistiksel olarak anlamlı olmamakla birlikte, balon atriyal septostomi, tüm bileşik skorlarda bir azalmaya yol açan tek faktör oldu. C-reaktif protein ile tüm bileşik skorlar arasında anlamlı bir negatif korelasyon izlendi. Ayrıca kardiyopulmoner baypas süresi, kros klemp süresi, ameliyat sonrası 2-5. günlerde ortalama plazma laktat seviyeleri (mmol/L), ameliyat sonrası kreatinin ve motor bileşik skorlar arasında anlamlı bir negatif korelasyon vardı. Büyüme ağırlığı ve baş çevresi ile tüm üç bileşik skor arasında anlamlı bir pozitif korelasyon tespit edildi.

Sonuç: Balon atriyal septostomi, yenidoğanlarda nörogelişimsel süreci olumsuz etkileyebilir. Ameliyat sonrası laktat, C-reaktif protein ve kreatinin gibi kan değerlerinin yakından takip edilmesinin ve hipoksemiden kaçınılmasının ve bu değerlerin optimal düzeylerde tutulmasının önemli olduğu kanaatindeyiz. İyi kilo alımı da hastaların nörogelişimine katkıda bulunabilir.

Anahtar sözcükler: Balon atriyal septostomi, Bayley-III skorlama sistemi, nörogelişimsel sonuçlar, büyük arter transpozisyonu.

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Congenital heart diseases (CHDs) affect millions of newborns every year worldwide.[1] Over the last few decades, with the developments in surgical technique and perioperative care, as well as the decrease in mortality in surgeries, a close interest has aroused in the process of neurodevelopment after cardiac surgery, particularly in neonates.[2-4] As surgical survival has increased, the focus of research has increasingly shifted from mortality to assessment of postoperative long-term morbidity. The 2nd edition of the Bayley Scales of Infant and Toddler Development (BSID-II) was used to evaluate development in infants and toddlers until 2006. Currently, the 3rd edition of the scale (Bayley-III) is widely used to evaluate neurodevelopment.[5,6]

McQuillen et al.[7] identified balloon atrial septostomy (BAS) as an important risk factor for preoperative focal brain damage in newborns with transposition of the great arteries (TGA).[7] Children with CHD demonstrate a high prevalence of developmental disorder, disabilities or developmental delay.[8] There are also studies that associate critical CHDs such as TGA with neurodevelopmental disorders and evaluate this as a process that begins *in utero*.[8-16] Studies on neurodevelopmental outcome in CHD are predominantly conducted in newborns with TGA. Individuals with TGA represent a unique and relatively homogeneous study cohort with the arterial switch operation (ASO) being now the standard-of-care. The only genetic syndrome with a strong relation with TGA is heterotaxy. Critical factors such as the rarity of the neurodevelopmental delay that may develop due to the genetic syndrome and the fact that there is a currently accepted standard surgical treatment make it easier to isolate the perioperative factors affect neurodevelopmental outcomes for patients with TGA.[17-19]

In the present study, we aimed to investigate the effect of preoperative BAS and intraoperative parameters on neurodevelopmental outcomes in patients operated for TGA using the Bayley-III scoring.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dr. Gazi Yaşargil Training and Research Hospital, Department of Pediatric Cardiac Surgery between February 2018 and March 2022. A total of 60 patients (49 male, 11 female; mean age, 23.5±8.8 days; range, 2 to 106 days) who were operated with a diagnosis of simple TGA and discharged uneventfully were included. Exclusion criteria were as follows: Parents of the patients did not answer any call attempts or refused to participate in the study. The patients were divided into two groups according to the application of preoperative BAS. Thirty-three patients required BAS, while 27 patients did not undergo BAS. A written informed consent was obtained from the parents and/or legal guardians of the patients. The study protocol was approved by the Dr. Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (date: 14.07.2023, no: 460). The study was conducted in accordance with the principles of the Declaration of Helsinki.

A pediatric cardiologist evaluated all neonates with TGA preoperatively to determine the need for a BAS. The indication for BAS was based on systemic arterial oxygen saturation (SaO_2), clinical assessment of cardiac output, and patency/size of the interatrial communication by echocardiography.[7] Typically, BAS was performed in the cardiac catheterization laboratory under fluoroscopic guidance with hemodynamic monitoring. Medical records of the patients were reviewed retrospectively to determine the accuracy and completeness of the information available. Afterwards, nine months and older children were invited to the Child Development outpatient clinic to assess their neurodevelopment using the Bayley-III scoring system. Follow-up status for neurodevelopment was considered to be incomplete, if the parents of the patients did not answer any call attempts or refused to participate in the study. Finally, 13 patients in the septostomy group (BAS+) and 12 patients in the non-septostomy group (BAS–) were admitted to the outpatient clinic to assess their neurodevelopment. The neurodevelopment of these two groups was evaluated and the parameters that may affect this development were investigated. The Bayley-III, (Bayley-III™ Screening Test, PsychCorp-Harcourt, Brace, & Co, TX, USA) was administered. The scale consists of three primary composite standard scores, the cognitive, motor, and language composite scores (CS), measured by performance of specified tasks, and scored against a normative population, scaled to have a mean score of 100 with standard deviation of 15. The age of the patients at the time of the application of the CS tests ranged between nine and 44 months. In addition, an extensive parental questionnaire was administered. Socioeconomic status was classified as below minimum wage, minimum wage, and above minimum wage. These tests were administered by a single developmental behavioral pediatrician. The Bayley-III cognitive, language, and motor CS were

Table 1. Comparison of all parameters according to preoperative need for BAS

	BAS (+)			BAS (–)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age at the time of composite score testing (month)			24.46±6.35			22.25±11.69	0.569**
Sex							0.051
Female	2	15		5	41.6		
Male	11	85		7	58.4		
Socioeconomic status							**0.043**
Below minimum wage	7	53.8a		1	8.3b		
Minimum wage	3	23.1a		7	58.3a		
Above minimum wage	3	23.1a		4	33.3a		
Mother's schooling							0.063
Less than high school	12	92.3		8	66.7		
High school/some college	0	.0		4	33.3		
Completed college	1	7.7		0	0		
Ongoing chronic illness							0.689
+	3	23.1		2	16.7		
–	10	76.9		10	83.3		
Chromosomal abnormality							1.000
+	1	8.3		0	0		
–	12	91.7		12	100.0		
Birth gestation (week)			39.13±2.01			38.79±1.44	0.115***
Birth weight (g)			3186.77±648.19			3199.38±391.36	0.933**
Weight at the time of operation (g)			3267.50±503.60			3220.83±409.91	0.712**
Primary surgery age (day)			15.00±17.01			11.24±5.74	0.199***
Number of therapies/surgeries ≤12 months (more than 1)							0.931
+	0	0		0	0		
–	13	100		12	100.0		
CPB time (min)			199.18±37.13			191.57±29.07	0.441**
CC time (min)			125.07±24.68			128.24±20.80	0.637**
Temperature nadir (degrees)			28.12±.070			28.16±0.80	0.842***
NICU length of stay (day)			27.64±19.86			21.96±8.55	0.157***
Ventilation time (day)			6.45±6.03			4.96±7.31	0.051***
Hospital length of stay (day)			33.67±20.03			26.08±9.22	0.062***
Postoperative Day 1, highest plasma lactate (mmol/L)			5.12±3.15			4.85±3.89	0.778**
Postoperative Day 1, lowest arterial pH			7.34±0.12			7.37±0.10	0.420**
Postoperative Day 1, lowest PaO_2 (mmHg)			64.46±23.49			64.20±24.85	0.968**
Convulsion							0.431
+	0	0		0	0.0		
–	13	100.0		12	100.0		
CPR							0.501
+	1	8.3		0	0		
–	12	91.7		12	100.0		
Dialysis							0.181
+	0	0		1	8.0		
–	13	100.0		11	9.0		
Brain imaging							0.921
+	2	15.3		2	16.0		
–	11	84.7		10	84.0		

Table 1. Continued

	BAS (+)			BAS (–)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Postoperative Days 2-5, mean plasma lactate (mmol/L)			2.06±0.73			1.87±.65	0.304***
Postoperative Days 2-5, lowest arterial pH			7.31±0.09			7.29±0.11	0.577**
Postoperative Days 2-5, lowest PaO_2 (mm Hg)			50.15±6.47			52.59±6.47	0.223***
HCT (postoperative)			39.42±5.63			38.85±5.70	0.704**
HGB (postoperative)			13.15±1.89			13.20±1.94	0.929**
WBC (postoperative)			9.78±4.45			10.90±4.21	0.212***
NEU (postoperative)			6.84±3.72			7.52±3.41	0.162***
LYM (postoperative)			2.00±1.01			2.30±1.06	0.275**
PLT (postoperative)			137575.76±75005.43			136120.00±50463.95	0.826***
ALB (postoperative)			3.43±0.50			3.41±0.56	0.896**
AST (postoperative)			140.91±60.91			133.60±55.14	0.626***
ALT (postoperative)			12.33±7.28			13.56±6.28	0.305***
UREA (postoperative)			20.03±15.81			24.78±21.23	0.332**
CRE (postoperative)			0.69±0.13			0.66±0.13	0.444**
CRP (postoperative)			3.58±3.47			4.20±8.04	0.392***
Growth Weight (Z-score)			–1.15±1.49			–0.88±0.83	0.589**
Length (Z-score)			–0.46±1.44			–0.97±0.88	0.300**
Head circumference (Z-score)			–1.54±1.36			–1.69±1.21	0.776**
Cognitive composite score			85.00±11.73			94.58±18.40	0.131**
Language composite score			89.62±12.29			99.83±15.71	0.123***
Motor composite score			83.38±14.83			90.00±18.73	0.689***

BAS: Balloon atrial septostomy; SD: Standard deviation; CPB: Cardiopulmonary bypass; CC: Cross-clamp; NICU: Neonatal intensive care unit; CPR: Cardiopulmonary resuscitation; HCT: Hematocrit; HGB: Hemoglobin; WBC: White blood cell; NEU: Neutrophils; LYM: Lymphocytes; PLT: Platelets; ALB: Albumin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CRE: Creatinine; CRP: Cardiopulmonary bypass; * Chi-square analysis; ** Student t test; *** Mann Whitney U-test was applied; a, b: The group from which the difference originates

completed for all patients.[6] Cognitive, language or motor CS <85 was taken as mild impairment /at risk of development delay.[20]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The Pearson chi-square test was used to compare categorical variables between groups. In cases where a significant difference was observed, the Bonferroni correction was applied as a *post-hoc* analysis. The conformity of continuous variables to normal distribution was evaluated by the Shapiro-Wilk test. The Student t-test was used for variables with normal distribution and Mann-Whitney U test was used for variables without normal distribution. The Pearson correlation test was used for variables with normal distribution and Spearman correlation test was used for variables without normal distribution. Linear regression analysis was applied to determine the predictors of neurological values. The enter method was used to create the model and those with significant correlation in the correlation test were included in the model. A p value of <0.05 was considered statistically significant.

Table 2. Neurodevelopmental findings' correlation of patients admitted to child development outpatient clinic

	Cognitive composite score	Language composite score	Motor composite score
Language composite score			
r	**0.834**		
p	**<0.001**		
Motor composite score			
r	**0.437**	0.250	
p	**0.029**	0.228	
Age (month)			
r	0.058	0.017	–0.074
p	0.783	0.936	0.727
Birth gestation (week)			
r	0.314	**0.490**	0.189
p	0.135	0.015	0.376
Birth weight (kg)			
r	0.335	0.170	0.331
p	0.110	0.428	0.114
Weight at the time of operation (kg)			
r	0.387	0.191	0.339
p	0.062	0.372	0.105
Primary surgery age (day)			
r	0.077	0.099	0.079
p	0.720	0.645	0.713
CPB time (min)			
r	–0.273	–0.169	**–0.527**
p	0.274	0.502	**0.025**
CC time (min)			
r	–0.247	–0.096	**–0.538**
p	0.322	0.704	**0.021**
Temperature nadir (degrees)			
r	–0.088	–0.263	–0.142
p	0.683	0.214	0.507
NICU length of stay (day)			
r	–0.285	–0.389	–0.351
p	0.178	0.060	0.092
Ventilation time (day)			
r	–0.111	–0.253	–0.316
p	0.605	0.233	0.132
Hospital length of stay (day)			
r	–0.287	–0.378	–0.361
p	0.174	0.068	0.083
Postoperative day 1 highest plasma lactate (mmol/L)			
r	0.177	0.022	–0.265
p	0.407	0.918	0.210
Lowest arterial pH (postoperative)			
r	0.178	**0.498**	–0.187
p	0.404	**0.013**	0.381

Table 2. Continued

	Cognitive composite score	Language composite score	Motor composite score
Lowest PaO_2 (mmHg) (postoperative)			
r	0.029	0.147	0.087
p	0.894	0.494	0.686
Postoperative day 2–5, mean plasma lactate (mmol/L)			
r	–0.386	–0.206	**–0.499**
p	0.062	0.335	0.013
Lowest arterial pH (postoperative)			
r	–0.018	0.116	–0.093
p	0.933	0.589	0.665
Lowest PaO_2 (mmHg) (postoperative)			
r	0.205	0.197	0.077
p	0.338	0.357	0.721
HCT (postoperative)			
r	0.397	0.219	0.089
p	0.055	0.304	0.680
HGB (postoperative)			
r	**0.464**	0.323	0.124
p	**0.022**	0.123	0.564
WBC (postoperative)			
r	0.379	0.184	0.319
p	0.068	0.389	0.129
NEU (postoperative)			
r	0.399	0.187	0.400
p	0.053	0.381	0.053
LYM (postoperative)			
r	0.150	0.051	–0.077
p	0.484	0.812	0.721
PLT (postoperative)			
r	–0.047	–0.243	0.096
p	0.826	0.252	0.655
ALB (postoperative)			
r	–0.112	0.029	–0.104
p	0.601	0.892	0.627
AST (postoperative)			
r	–0.299	–0.311	–0.360
p	0.156	0.140	0.084
ALT (postoperative)			
r	–0.047	–0.273	0.168
p	0.827	0.197	0.432
UREA (postoperative)			
r	–0.259	–0.079	–0.231
p	0.222	0.714	0.277
CRE (postoperative)			
r	–0.309	–0.186	–0.429
p	0.142	0.385	0.036

Table 2. Continued

	Cognitive composite score	Language composite score	Motor composite score
CRP (postoperative)			
r	**–0.467**	**–0.444**	**–0.493**
p	**0.021**	**0.030**	**0.014**
Growth weight			
r	**0.640**	**0.554**	**0.473**
p	**0.001**	**0.004**	**0.017**
Length			
r	0.326	0.163	**0.577**
p	0.111	0.437	**0.003**
Head circumference (Z-score)			
r	**0.675**	**0.596**	**0.45**
p	**<0.001**	**0.002**	**0.023**

CPB: Cardiopulmonary bypass; CC: Cross-clamp; NICU: Neonatal intensive care unit; HCT: Hematocrit; HGB: Hemoglobin; WBC: White blood cell; NEU: Neutrophils; LYM: Lymphocytes; PLT: Platelets; ALB: Albumin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CRE: Creatinine; CRP: C-reactive protein.

RESULTS

In this study, both groups were balanced in terms of parameters affecting neurodevelopment, except for socioeconomic status. There was no statistically significant difference in the sex distribution and mean age between the groups (p=0.051 and p=0.569, respectively). However, the socioeconomic status of the BAS+ group was significantly lower than the socioeconomic status of the BAS– group (p=0.043). According to the post-hoc analysis, this difference originated from the part below the minimum wage. Although not statistically significant, all three cognitive, language and motor CS were significantly lower in the BAS+ group (p>0.05). No significant difference was observed between the groups in terms of other parameters such as mother's education status, socioeconomic status, intraoperative parameters, blood parameters, CS, and neonatal intensive care unit (NICU) parameters (p>0.05) (Table 1). Postoperative brain imaging was planned for patients with hydrocephalus, chromosomal abnormality or intracranial bleeding. Two patients in the BAS+ group needed >1 therapies or surgeries before 12 months due to ventriculoperitoneal shunt for hydrocephalus and right diaphragm plication (Table 1).

Although there was a significant positive correlation between cognitive CS and hemoglobin, growth weight, head circumference (Z-score), there was a significant negative correlation between cognitive CS and C-reactive protein (CRP) (r=–0.467, p=0.021). There was a significant positive correlation between language CS and gestational age (weeks), lowest arterial pH, growth weight and head circumference (Z-score) and a significant negative correlation between language CS and CRP (r=–0.444, p=0.030). There was a significant positive correlation between motor CS and growth weight, length and head circumference (Z-score), and a significant negative correlation between motor CS and cardiopulmonary bypass (CPB) time (min), cross-clamping (CC) time (min), mean plasma lactate (mmol/L) on postoperative Days 2-5, creatinine (CRE) and CRP (r=–0.493, p=0.014) (Table 2).

According to the multiple linear regression analysis, cognitive CS could predict language CS (β=0.588, p<0.001) and motor CS (β=0.332, p=0.005). Language CS predicted cognitive CS (β=0.636, p<0.001) (Table 3).

DISCUSSION

In the present study, we investigated the effect of preoperative BAS and intraoperative parameters on neurodevelopmental outcomes in patients operated for TGA using the Bayley-III scoring. Our study results showed that BAS was the only factor which caused a decrease in all CSs according to Bayley-III scoring, although not statistically significant, and also there were some intraoperative parameters showing an association with poor

Table 3. Linear regression analysis of factors associated with cognitive, language, and motor composite score

	β	SE	Standard β	t	*p*	VIF
Cognitive composite score (R^2=0.812; F=17.596; p<0.001)						
Language composite score	0.588	0.132	0.556	4.453	<0.001	1.910
Motor composite score	0.332	0.103	0.386	3.215	0.005	1.768
HGB (postoperative)	1.274	0.841	0.167	1.515	0.148	1.482
CRP (postoperative)	0.874	2.108	0.049	0.415	0.684	1.705
Growth weight	0.432	2.071	0.035	0.209	0.837	3.452
Head circumference (Z-score)	0.504	1.948	0.043	0.259	0.799	3.314
Language composite score (R^2=0.747; F=12.335; p<0.001)						
Cognitive composite score	0.636	0.147	0.673	4.321	<0.001	2.210
Birth gestation (week)	1.743	0.859	0.275	2.031	0.058	1.668
Lowest arterial pH (postoperative)	24.241	20.142	0.146	1.203	0.245	1.335
CRP (postoperative)	–2.126	2.316	–0.126	–0.918	0.372	1.712
Growth weight	0.157	2.280	0.013	0.069	0.946	3.481
Head circumference (Z-score)	–1.061	2.271	–0.095	–0.467	0.646	3.747
Motor composite score (R^2=0.471; F=2.581; p=0.112)						
Cognitive composite score	0.650	0.477	0.564	1.363	0.215	5.170
CPB time (min)	–0.056	0.441	–0.096	–0.126	0.903	17.543
CC time (min)	–0.112	0.732	–0.131	–0.153	0.883	22.141
Postoperative day 2-5, mean plasma lactate (mmol/L)	–5.492	17.054	–0.125	–0.322	0.757	4.547
CRE (postoperative)	–14.439	57.854	–0.108	–0.250	0.810	5.677
CRP (postoperative)	2.352	6.157	0.116	0.382	0.714	2.796
Growth weight	–2.630	7.409	–0.182	–0.355	0.733	7.956
Length	1.517	3.800	0.108	0.399	0.702	2.231
Head circumference (Z-score)	4.852	8.852	0.290	0.548	0.601	8.464

SE: Standard error; VIF: Variance inflation factor; HGB: Hemoglobin; CRP: C-reactive protein; CPB: Cardiopulmonary bypasss; CC: Cross-clamp; CRE: Creatinine.

neurodevelopmental outcomes. Initially, a total of 60 patients were included in the study; however, the sample size decreased as some patients could not be reached, moved to another city, returned to their country of origin or refused attendance to follow-up visits. Therefore, we were able to assess neurodevelopmental processes of 13 patients in the BAS+ group and 12 patients in the BAS– group. There was no statistically significant difference between the two groups except for the socioeconomic status: the parents of the BAS patients had a lower socioeconomic status. Considering postoperative data including lactate, oxygenation, NICU stay, cardiopulmonary resuscitation (CPR) application, CRE, and ventilation time, there was no significant difference between the two groups. Furthermore, we did not observe any significant difference between intraoperative CC and CPB times and no patient needed extracorporeal membrane oxygenation (ECMO).

In their study, McQuillen et al.[7] identified BAS as an important risk factor for preoperative acquired brain injury in neonates with TGA. Although we were unable to find statistically significant difference in our study, all three cognitive, language and motor CS were significantly lower in the BAS+ group. Of note, we cannot exclude the fact that the patients who underwent BAS were more exposed to hypoxia and cyanosis in this process; however, we had two groups that were balanced in terms of parameters affecting neurodevelopment in many respects, except for the socioeconomic status. Initially, 25 patients (13 BAS+, 12 BAS–) were

admitted to Child Development outpatient clinic and their neurodevelopmental process was evaluated using the Bayley-III scoring system. Their data and its relation with CS and BAS were calculated statistically and we reached some conclusions that may be related to neurodevelopment. First, BAS was the only factor that caused a significant decrease in all three of the cognitive, language and motor CS according to Bayley-III scoring, although not statistically significant. The mean cognitive, language, motor CS were 85.00±11.73, 89.62±12.29, 83.38±14.83, respectively in the BAS+ group and 94.58±18.40, 99.83±15.71, 90.00±18.73, respectively in the BAS– group.

In the current study, we also observed a significant negative correlation between CRP, a routine blood test taken postoperatively in NICU, and all three cognitive, language and motor CS. There is also evidence that CRP, a marker of systemic inflammation, is associated with an increased risk for cognitive decline in adults.[21] There was a significant negative correlation between CPB and CC time, the mean plasma lactate (mmol/L) on postoperative Days 2-5, postoperative CRE and motor CS. However, Algra et al.[22] found no statistically significant relation between CPB time, the mean-highest arterial lactate (mmol/L), and new white matter injury in their cohort. There was a significant positive correlation between growth weight and head circumference (Z-score) and all three cognitive, language, and motor CS.

In another study, Acton et al.[23] evaluated a different ASO cohort from our study, using the Bayley-III. The mean cognitive composite standard score was 101.4±1.6, language composite standard score was 97.4±17.2, and motor composite standard score was 99.8±10.5. In their study, deep hypothermic circulatory arrest was used as the surgical technique in approximately 70% of the cohort. Patients who required ECMO and those with chromosomal abnormalities were excluded.

As improvements in neonatal heart surgery have allowed us to significantly lower operative mortality, a normal neurodevelopment has become an equally important goal. Andropoulos et al.[24] reported their neurological outcomes after neonatal ASO. They had 100% survival rate and favorable neurodevelopmental outcomes (cognitive: 104.8±15.0, language: 90.0 [83.0-94.0], motor: 92.3±14.2), consistent with our findings. The authors emphasized the importance of pre-, intra-, and postoperative monitoring of regional cerebral oxygen saturation, and keeping that saturation above 50%. In our cohort, we attribute the relatively low CS in the BAS+ group to preoperative low oxygen levels. Also, we had a non-modifiable factor such as socioeconomic status. The socioeconomic status of the BAS+ group was significantly lower than the socioeconomic status of the BAS– group, which probably contributed to the low CS in the BAS+ group.

Comparison of the current patient cohort with previous reports of neurodevelopmental outcomes in neonatal ASO patients is problematic, as previous versions of the BSID are significantly different and direct transfer of scores between different versions is not possible.[23,25] However, the developmental pediatrics and psychological experts, including our own coauthor, caution against this and would state that the Bayley-III really is more comprehensive test. Currently, the Bayley-III is the most frequently used standardized developmental tool for assessing development in infancy and early childhood in both clinical practice and research settings. It provides more detailed and precise information than BSID-II in terms of separately evaluating the child's cognitive, receptive language, expressive language, fine motor and gross motor skills.[6] Celik et al.[26] conducted a study comparing BSID-II and Bayley-III in Turkish children and commented that the scores in Bayley-III were relatively higher than those in BSID-II. However, there is also literature describing an overestimation of neurodevelopmental problems with the BSID-II.[23,27,28] While approximately 10% of the standardization of Bayley-III has been done in children with developmental difficulties or delays, the standardization of BSID-II has been done completely in healthy children. This may result higher rates of developmental delay in BSID-II. In other words, BSID-II may have been mildly pessimistic.[29]

In our center, the ASO for simple TGA is performed during the first two weeks of life, except in the setting of prematurity or when preoperative complications delay surgery. Mortality rates in this patient group tend to decrease and it is becoming more important for patients to live with normal neurodevelopment.[24] In our cohort, children after ASO had neurodevelopmental outcomes at expected levels for their age. This once again emphasizes the importance of perioperative care. We believe that close monitoring of postoperative blood values such as lactate, CRP, CRE, avoiding hypoxemia and keeping them at optimal levels are of utmost importance. Good weight gain can also contribute

to the neurodevelopment of patients. Consistent with the literature, we believe that BAS has a negative effect on development.

Nonetheless, there are some limitations to this study. There is growing evidence supporting that anatomical and functional neurodevelopmental impairments, which possibly caused by impaired oxygen distribution to the brain, are also present before surgery indicated by magnetic resonance imaging (MRI) findings.[30] This may be a limitation for us, as we have no MRI findings in our study. The wide age range between nine and 44 months may be another limitation. The small size of the cohort also should be noted since it confines the strength of our results.

In conclusion, close monitoring of postoperative blood values such as lactate, C-reactive protein and creatinine, and avoiding hypoxemia and keeping them at optimal levels are crucial in this group of patients. Good weight gain can also contribute to the neurodevelopment of patients and balloon atrial septostomy may adversely affect the neurodevelopmental process. Further multi-center, large-scale, prospective studies are needed to confirm these findings and to aid in designing appropriate interventional trials.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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