JPPT | Single Center Retrospective Study

Novel Dosing and Monitoring of Aspirin in Infants With Systemic-to–Pulmonary Artery Shunt Physiology: the SOPRANO Study

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OBJECTIVES Provision of pulmonary blood flow with a systemic-to–pulmonary artery shunt is essential in some patients with cyanotic congenital heart disease. Traditionally, aspirin (ASA) has been used to prevent thrombosis. We evaluated ASA dosing with 2 separate antiplatelet monitoring tests for accuracy and reliability.

METHODS This is a retrospective, pre-post intervention single center study. Two cohorts were evaluated; the pre-intervention group used thromboelastography platelet mapping (TPM) and post-intervention used VerifyNow aspirin reactivity unit (ARU) monitoring. The primary endpoint was to compare therapeutic effect of TPM and ARU with regard to platelet inhibition. Inadequate platelet inhibition was defined as TPM <50% inhibition and ARU >550.

RESULTS Data from 49 patients were analyzed: 25 in the TPM group and 24 in the ARU group. Baseline characteristics were similar amongst the cohorts. The TPM group had significantly more patients with inadequate platelet inhibition (14 [56%] vs 2 [8%]; p = 0.0006) and required escalation with additional thromboprophylaxis (15 [60%] vs 5 [21%]). There was no difference in shunt thrombosis (1 [2%] vs 0 [0%]; p = 0.32), cyanosis requiring early re-intervention (9 [36%] vs 14 [58%]; p = 0.11), or bleeding (15 [60%] vs 14 [58%]; p = 0.66).

CONCLUSION With similar cohorts and the same ASA-dosing nomogram, ARU monitoring resulted in a reduced need for escalation of care and concomitant thromboprophylaxis with no difference in adverse outcomes. Our study suggests ARU monitoring compared with TPM may be a more reliable therapeutic platelet inhibition test for determining ASA sensitivity in children with congenital heart disease requiring systemic-to–pulmonary artery shunt.

ABBREVIATIONS AA, arachidonic acid; ARU, VerifyNow aspirin reactivity unit; ASA, aspirin; CHD, congenital heart defect; GI, gastrointestinal; IMPACT, Improving Pediatric and Adult Congenital Treatments Registry; KDIGO, Kidney Disease: Improving Global Outcomes; mBTTs, modified Blalock-Taussig-Thomas shunts; STS, Society of Thoracic Surgeons; SV, single ventricle; TPM, thromboelastography platelet mapping; UFH, unfractionated heparin

KEYWORDS aspirin; congenital heart disease; platelet inhibition; shunts; thrombosis

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Introduction

In the United States, congenital heart defects (CHDs) are the most common birth defects and account for a large number of infant deaths within the first year of life.[1,2] Shunts are most commonly placed for primary palliation or as a component of staged reconstruction in infants with single-ventricle (SV) physiology.[3] Provision of pulmonary blood flow with a systemic-to–pulmonary artery shunt remains an essential component of initial treatment for some forms of complex cyanotic congenital heart disease.[4] Infants with cyanotic congenital heart disease palliated with placement of a systemic-to–pulmonary artery shunt are at an increased risk for thromboembolic events with the incidence being reported as high as 25% to 40%.[5,6]

Aspirin (ASA) is commonly used as thromboprophylaxis in patients requiring a systemic-to–pulmonary artery shunt and is associated with a greater than 7-fold reduction in the risk of shunt thrombosis and a decreased risk of death.[7] However, there is a paucity of data regarding the optimal dose, monitoring, and effectiveness of ASA in congenital heart disease.

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Dosing is largely extrapolated from adult studies and small heterogeneous studies, and when to initiate enteral ASA in the postoperative period is also debated.[8] Given these concerns, use of antiplatelet monitoring is crucial to ensure adequate ASA response. There are many reported ways to monitor ASA response, including ASA urine metabolite testing, light-transmission aggregometry, and platelet mapping. Two commonly used antiplatelet tests are thromboelastography platelet mapping (TPM) and VerifyNow aspirin reactivity units (ARUs; Accumetrics, San Diego, CA), but the evidence supporting these methods is quite varied with significant interpatient variability in response to the same weight-based ASA dosing.[3,9] A phenomenon called *aspirin resistance* has been seen in infants with CHDs, defined in previous studies using a combination of TPM and urine thromboxane concentrations.[4] However, the incidence of ASA resistance or inadequate platelet inhibition reported has significantly varied between studies using TPM compared with ARU.[4,10]

The objective of this study was to compare these 2 antiplatelet monitoring tests in SV patients palliated with a systemic-to–pulmonary artery shunt with regard to therapeutic effect. Additionally, this study assessed the safety and efficacy of our institutions' ASA-dosing nomogram.

Materials and Methods

Patients and Study Design. This is a retrospective, pre-post intervention single center study. The 2 cohorts (July 1, 2018–September, 30, 2019; and November 1, 2019–January 31, 2021) were evaluated before and after a practice change that varied by type of platelet monitoring. The pre-intervention group had antiplatelet effect measured by TPM, while the post-intervention group had antiplatelet effect measured with ARU. Both groups used the same novel ASA-dosing nomogram that stratified dosing by weight classifications (i.e., <2.5 kg received 20.25 mg, 2.5 kg–10 kg received 40.5 mg, >10 kg received 81 mg).

This study included neonates or infants aged <120 days at enteral ASA initiation with a cyanotic CHD palliated with a systemic-to–pulmonary artery shunt. They must have received enteral ASA for primary shunt thromboprophylaxis with a planned second-stage palliation. Patients were excluded if they had active bleeding, a known bleeding disorder, arteriovenous malformations, or previous intraventricular hemorrhage (grades II–IV). Patients were also excluded for clinically significant or persistent thrombocytopenia, neutropenia, severe hepatic failure (i.e., more than 2.5 times the upper limit for age of hepatic enzymes), or acute renal failure as defined by KDIGO (Kidney Disease: Improving Global Outcomes)[11] stage II or greater. Additionally, patients must be postmenstrual age >36 weeks. Patients were identified from the IMPACT Registry (IMproving Pediatric and Adult Congenital Treatments)[12] and Society of Thoracic Surgeons (STS) database.[13]

The primary endpoint was to compare therapeutic effect of TPM and ARU with regard to platelet inhibition. We evaluated the number of patients with therapeutic antiplatelet effect via TPM (defined as >50% inhibition of arachidonic acid [AA]) or ARU (defined as <550).[3,11] Additionally, we evaluated the number of patients who needed escalation of care with concomitant thromboprophylaxis or increased ASA dose for subtherapeutic platelet inhibition.

Secondary efficacy endpoints evaluated a composite score of thrombotic event rates, progressive cyanosis requiring cardiovascular unplanned intervention, and sudden cardiac-related death. Unplanned interventions for progressive cyanosis included predominately catheter-based interventions, with the possibility for surgical intervention if continued progression without improvement after catheterization. Secondary safety endpoints evaluated included minor bleeding, major bleeding, and composite bleeding. Minor bleeding was defined as bleeding requiring no intervention other than holding medication or monitoring; major bleeding was defined as requiring an intervention to treat bleeding (medical or surgical), and composite bleeding score. Composite bleeding was defined as the combination of all minor and major bleeding events amongst each cohort. Bleeding was evaluated retrospectively for each patient by chart review once they received their first dose of ASA through the duration the systemic-to–pulmonary artery shunt was present.

Anticoagulation Strategy. The study used a novel ASA-dosing nomogram for patients with cyanotic congenital heart disease palliated with placement of a systemic-to–pulmonary artery shunt. Patients were started immediately postoperatively on unfractionated heparin (UFH) 15 units/kg/hr while central venous line or intracardiac lines were in place. Once deemed stable postoperatively by the primary cardiac intensivist, patients were then started on enteral ASA with stratified dosing based on weight classifications (i.e., <2.5 kg received 20.25 mg, 2.5 kg–10 kg received 40.5 mg, >10 kg received 81 mg). In the pre-intervention group, antiplatelet effect was measured after 2 to 3 doses of ASA with TPM to target inhibition >50%. In the post-intervention group, antiplatelet effect was measured after 3 doses of ASA to target an ARU <550. If a patient was receiving 20.25 mg daily with a subtherapeutic TPM or ARU, the ASA dose was increased to 40.5 mg daily. If the patient was receiving 40.5 mg daily with a subtherapeutic TPM or ARU, thromboprophylaxis was added with systemic anticoagulation (i.e., enoxaparin or UFH) to prevent shunt thrombosis.

Statistical Analysis. All data are presented as median (IQR) for continuous variables, and count (%) for categorical variables. We used Wilcoxon rank sum tests for comparing medians, and Fisher exact tests

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to compare proportions between the TPM and ARU groups. Statistical significance was assessed at the 5% level, and all tests were 2-tailed. To investigate the association between bleeding events (bloody stool) and the various predictors, we performed univariate logistic regression. Variables to be included in the univariate regression were chosen by and agreed upon by the primary investigator and lead statistician. The composite secondary efficacy outcome is displayed via a Kaplan-Meier event rate curve. Variables with p values greater than 0.2 were inputted into the multivariable model but none showed statistical significance. All statistical analyses were performed in SAS 9.3 (Cary, NC).

Results

Seventy patient charts were identified from the study period; 49 patients were included for final analysis with 25 in the TPM group and 24 in the ARU group. All patients excluded either never received ASA or did not have platelet inhibition measured by TPM or ARU. Baseline characteristics were similar amongst the 2 groups with the exception of shunt type (Table 1). In the TPM group, there were significantly more modified Blalock-Taussig-Thomas shunts (mBTTs) than Sano shunts ([88%] vs 8 [33%] and 3 [12%] vs 15 [62%], respectively; p = 0.004). The TPM group had significantly more patients with inadequate platelet inhibition (14 [56%] vs 2 [8%]; p = 0.0006) and escalation of care with additional thromboprophylaxis (15 [60%] vs 5 [21%]; p = 0.005]. Between TPM and ARU, there was no difference in a composite efficacy endpoint including shunt thrombosis (1 [2%] vs 0 [0%]; p = 0.32], cyanosis requiring re-intervention (9 [36%] vs 14 [58%]; p = 0.11], or sudden death [5/25 vs 1/24; p = 0.19) (Table 2; Figure). There was also no difference in minor bleeding (14 [56%] vs 14 [58%]; p = 0.87), major bleeding (1 [4%] vs 0 [0%]; p = 0.32], or composite bleeding (15 [52%] vs 14 [58%]; p = 0.66]. The most common bleeding event was bloody stools with 13 (52%) reported in the TPM group and 13 (54%) reported in the ARU group (Table 3.). A univariate prediction analysis of bloody stools was completed and did not identify any independent risk factors (Table 4).

The TPM group started ASA significantly sooner postoperatively (day 7 vs day 11; p = 0.02) on significantly fewer feeds (24 mL/kg/day vs 95 mL/kg/day; p = 0.0004) with no difference in incidence of bloody stool (13 [52]) vs 13 [54]; p = 0.88]. The median dose of ASA was 12.3 mg/kg (IQR, 10.9–14) in the TPM group, compared with 13.5 mg/kg (IQR, 12.2–14.5) in the ARU group.

Discussion

Our study used 2 separate antiplatelet monitoring tests. Traditionally, SV patients receiving ASA were evaluated for ASA efficacy by TPM, which examined platelet aggregation in response to exogenous AA.[3] TPM provides an individualized percentage of inhibition to ASA when compared with a standardized reference range.[3] Newer methods, such as ARU, use embedded AA beads and light transmission aggregometry to qualitatively evaluate platelet inhibition compared with a manufacturer-recommended threshold.[14] Given there is no manufacturer-recommended minimum percentage of inhibition with regard to adequate platelet inhibition evaluated by TPM, efficacy was defined as greater than 50% inhibition of AA as previously reported by Mir et al.[3] We found patients monitored with TPM were often reported as having subtherapeutic platelet inhibition (14/25, 56%). This correlates with the incidence of previous findings of a synonymous phenomenon called *aspirin resistance*.[3] Given the concern for shunt thrombosis and sudden death, many of these patients were started on concomitant thromboprophylaxis with enoxaparin or UFH (15/25, 60%). After a practice change, our institution moved to ARU platelet inhibition testing for ASA.[9,10] Manufacturer recommendations for VerifyNow platelet aggregometry report a specificity of 100% and sensitivity of 91.4%, respectively, with an ARU of <550, at detecting ASA presence in adults receiving chronic ASA therapy of 81 mg daily.[14] This was further studied by Koh et al[10] who used an ARU cutoff of >550 to define ASA resistance in infants with shunt-dependent physiology.[10] Therefore, we defined efficacy as an ARU <550. We found that a much smaller rate of patients in the ARU group (2/24, 8%) was defined as achieving inadequate platelet inhibition compared with TPM, and subsequently fewer patients were on concomitant thromboprophylaxis (5/24, 21%). Given this finding in a similar patient population while using the same weight-based ASA-dosing nomogram and finding no difference in adverse outcomes, ARU may be a more appropriate therapeutic platelet inhibition test than TPM. Furthermore, ARU monitoring may reduce the unnecessary ASA dose increases and the addition of concomitant thromboprophylaxis. Further validation and comparison should be explored.

In addition to platelet inhibition, our study aimed to evaluate efficacy as defined by clinical outcomes. Adverse clinical outcomes in an infant palliated with a systemic-to–pulmonary artery shunt with regard to inadequate platelet inhibition can be acute or chronic.[5,6] Acutely, patients can experience shunt thrombosis and sudden cardiac death.[5] Chronically, intraluminal narrowing of the shunt via platelet aggregation and inflammation can result in cyanosis requiring early re-intervention, shunt thrombosis, or even sudden cardiac death.[5,6] Given the low incidence of these clinical outcomes, we used a composite score to evaluate the efficacy of our novel ASA-dosing nomogram, which included shunt thrombosis, cyanosis requiring early re-intervention, and sudden cardiac death. There was no

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Table 1. Baseline Patient Demographics

Baseline Demographics	TPM (n = 25)	ARU (n = 24)	p Value
Sex, male, n (%)	16 (64)	15 (63)	0.91
Age at surgery, median IQR, days	6 (4, 10)	6.5 (5, 7.5)	0.56
Race, n (%)			0.73
Black	12 (48)	13 (54)	
Hispanic	3 (12)	0 (0)	
White	10 (40)	11 (46)	
Weight, median (IQR), kg	3.2 (2.8–3.6)	3 (2.7–3.3)	0.16
Shunt type, n (%)			0.0004
Sano	3 (12)	15 (63)	
mBTT	22 (88)	8 (33)	
Other	0 (0)	1 (4)	
Chromosomal abnormality, n (%)			0.73
Yes	4 (16)	3 (12.5)	
No	21 (84)	21 (87.5)	
Congenital defect, n (%)			0.13
DILV	2 (8)	0 (0)	
HLHS	14 (56)	15 (62.5)	
PA/IVS	0 (0)	3 (12.5)	
Unbalanced AVC	6 (24)	2 (8.3)	
Other SV	3 (12)	4 (16.7)	

ARU, VerifyNow aspirin reactivity unit monitoring; AVC, atrioventricular canal; DILV, double inlet left ventricle; HLHS, hypoplastic left heart syndrome; mBTT, modified Blalock-Taussig-Thomas shunt; PA/IVS, pulmonary atresia with intact ventricular septum; SV, single ventricle; TPM, thromboelastography platelet mapping

statistical difference between the groups as displayed in a Kaplan-Meier event curve in the Figure.

Nationally accepted dosing of ASA for shunt prophylaxis in this patient population is 3 to 10 mg/kg, based on the type of shunt.[8] Based on available dosage forms, institutions using enteral formulations are forced to choose between halved or quartered 81-mg tablets because most of these patients have surgical palliation in the first month of life. We developed a novel dosing nomogram to stratify patients to fractional tablets by weight. While ensuring an adequate antiplatelet dose with ASA, providers must weigh concern for gastrointestinal (GI) bleeding risk secondary to the COX inhibition of prostaglandins, which protect the mucosal lining.[15–18] The mean weight across our study population was 3.1 kg (IQR, 2.8–3.4), and the mean ASA dose was 12.7 mg/kg (IQR, 11.6–14.4). While there was no difference in GI bleeding between the TPM and ARU group, overall, our study population had a high GI bleeding rate (n = 26 [53%]). Single-ventricle patients despite shunt type often have decreased GI perfusion.[19,20] It is plausible that larger doses of ASA (>10 mg/kg/dose) may cause significant mucosal prostaglandin inhibition, putting patients at a higher risk of mucosal injury.[21] However, a univariate predictive analysis of bloody stools showed no independent predictor including absolute or weight-based ASA dose (Table 4). No independent risk factor for GI bleeding was identified. Given our findings of low rate of shunt thrombosis with high rate of GI bleeding, the weight threshold for increasing from 20.25-mg ASA to 40.5-mg ASA should be studied further.

A major unanswered clinical question that often arises in the pediatric cardiac intensive care unit is in relation to enteral medication administration and enteral feeding volume. Practice varies throughout the country in regard to volume of enteral feeds a patient must be receiving prior to administration of enteral medications. Given the previously discussed concern for mucosal injury with ASA, administration on minimal to no enteral feeds is typically avoided.[22] Delay in ASA administration during the immediate postoperative period, when a patient with a systemic-to–pulmonary artery shunt is at the highest risk of thrombosis, can increase the risk for shunt thrombosis and in-stent stenosis.[5,6] Currently these patients undergo bridging therapy with low-dose UFH; however, it is not known if this offers the same antiplatelet and anti-inflammatory

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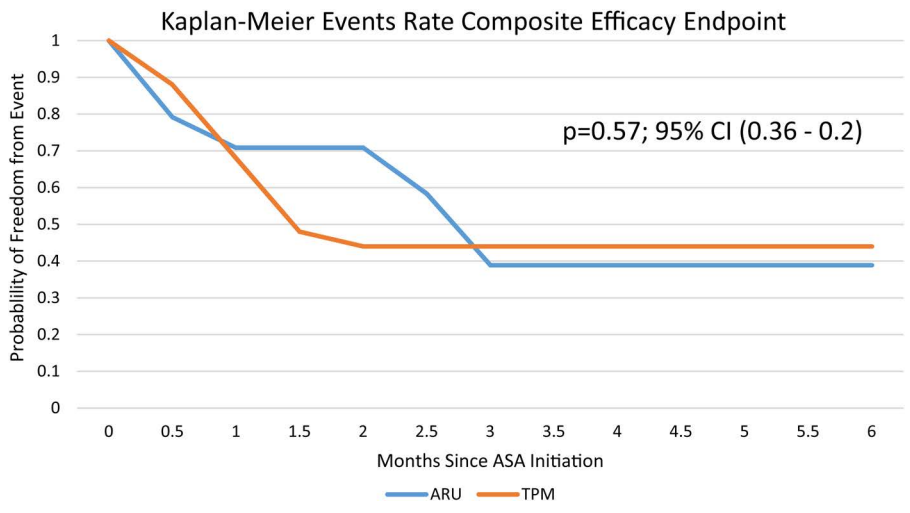
Table 2. Primary Results

Primary Endpoints	TPM (n = 25)	ARU (n = 24)	p Value
Shunt thrombosis, n (%)	1 (4)	0 (0)	0.32
Cyanosis requiring early re-intervention, n (%)	9 (36)	14 (58.3)	0.11
Age at re-intervention, median (IQR), days	28 (21–37)	46 (11–78)	0.87
Sudden cardiac death, n (%)	5 (20)	1 (4)	0.19
Inadequate platelet inhibition*	14 (56)	2 (8)	0.0004
ASA dose total mg, n (%)			0.32
40.5 mg	22 (88)	23 (95.8)	
Other	3 (12)	1 (4.2)	
ASA dose, median (IQR), mg/kg	12.3 (10.9–14)	13.5 (12.2–14.5)	0.10

ARU, VerifyNow aspirin reactivity unit monitoring; ASA, aspirin; TPM, thromboelastography platelet mapping

* Inadequate platelet inhibition: TPM inhibition <50%; ARU inhibition >550.

Figure. Kaplan-Meier event rate composite efficacy outcome.



ARU, VerifyNow aspirin reactivity unit monitoring; ASA, aspirin; TPM, thromboelastography platelet mapping.

benefits as ASA. Our study found that the TPM group received ASA significantly earlier postoperatively while receiving significantly fewer enteral feeds than the ARU group. This finding is likely due to a change in provider practice during the study period, but cannot be fully quantified. Despite this finding, the 2 groups had no difference in GI bleeding and thus withholding ASA, based on a specific enteral feeding volume goal, may not be necessary.

There are notable limitations to this study. A major difference in the baseline demographics to include shunt type between our 2 patient groups, TPM and ARU, was noted. The TPM group had significantly more mBTTs than the ARU group, while the ARU group had significantly more Sano shunts than the TPM group. This difference is due to a practice shift in surgical leadership and technique preference during the study period. In this patient population, Sano shunts were associated with increased transplant-free survival at 12 months when compared with the mBTTs; however, the Sano shunts had more unintended interventions and complications.[23] Given our TPM group had significantly more patients with mBTTs,

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Table 3. Secondary Results

Secondary Endpoints	TPM (n = 25)	ARU (n = 24)	p Value
Minor bleeding, n (%)	14 (56)	14 (58.3)	0.87
Major bleeding, n (%)	1 (4)	0 (0)	0.32
Composite bleeding, n (%)	15 (60)	14 (58.3)	0.66
Bloody stool, n (%)	13 (52)	13 (54.2)	0.88
Age at bleeding, median (IQR), days	38.5 (23–70)	42 (29–83)	0.65
Day of feeds initiation, median (IQR)	7 (5–9)	11 (5.5–16.5)	0.02
Amount of feeds on ASA administration, median (IQR), mL/kg	24 (14–54)	95 (52.5–123)	0.0004

ARU, VerifyNow aspirin reactivity unit monitoring; ASA, aspirin; TPM, thromboelastography platelet mapping

Table 4. Univariate Predictors of Bloody Stool

Univariate Predictors of Bloody Stool	OR	95% CI	p Value
Age at surgery	0.054	0.936–1.187	0.386
Sex (reference = female)	1.170	0.365–3.762	0.790
Chromosomal abnormality	0.152	0.017–1.370	0.093
Weight	1.290	0.471–3.522	0.920
ASA dose per kg	1.077	0.881–1.316	0.471
Syndrome	0.398	0.103–1.530	0.180
Race (Black vs Other)	0.659	0.213–2.039	0.470
Congenital defect (HLHS vs other)	0.877	0.280–2.750	0.822
ASA dose (40.5 mg vs other)	1.143	0.148–8.841	0.898
Shunt type (Sano vs other)	1.731	0.536–5.587	0.359
Thromboprophylaxis (Yes vs No)	1.231	0.393–3.856	0.715
Age at thromboprophylaxis	1.008	0.972–1.046	0.657
Day of initiation of feeds	1.038	0.944–1.141	0.442
Feeds amount at initiation	1.002	0.990–1.015	0.715
Group (ARU vs TPM)	1.091	0.355–3.352	0.879
TPM inhibition	0.993	0.959–1.038	0.685

ARU, VerifyNow aspirin reactivity unit monitoring; ASA, aspirin; HLHS, hypoplastic left heart syndrome; TPM, thromboelastography platelet mapping

but also with concomitant thromboprophylaxis owing to inadequate TPM platelet inhibition, this may have affected the composite outcome of our study.

Our study evaluated groups separately by the type of antiplatelet monitoring they used to quantify antiplatelet response: TPM or ARU. The type of monitoring changed during the study period, therefore no patients received both TPM and ARU monitoring. Additionally, there are few studies that compare the sensitivity and specificity between TPM and ARU, with varying results.[24–26] The lack of adequate comparative studies makes validation of an individual platelet inhibition assay difficult. Given we did not have both types of monitoring for each patient, we were unable to correlate TPM and ARU for individual patients. However, the demographics were similar and the dosing nomogram was the same throughout the

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study period; therefore, we can infer that the response to ASA should be similar between the 2 groups.

Additionally, our study used a novel ASA-dosing nomogram that ultimately resulted in aggressive weight-based dosing. Our average dose of ASA of 12.7 mg/kg across the study population was higher than the recommendations found in most literature of 3 to 10 mg/kg.[8] Our aggressive dosing may have skewed our efficacy and safety results; however, both the TPM and ARU groups received dosing according to the same nomogram. Lastly, sample size and power calculations were not performed. This is largely due to the predetermined intervention groups based on practice change; however, without a power calculation we cannot rule out the possibility of type I or type II error.

Conclusion

Use of ARU monitoring compared with TPM resulted in more consistent results and a reduction in the need for concomitant thromboprophylaxis. Using our ASA-dosing nomogram, the rates of shunt thrombosis and cyanosis requiring early re-intervention were low; however, rates of bloody stool were high in both groups. Given this finding, further studies should be done to determine the optimal ASA-dosing threshold. Timing of administration postoperatively did not correlate with bleeding despite significant differences in quantity of enteral feeds. Our study suggests ARU may be more reliable than TPM for determining ASA sensitivity in children with congenital heart disease requiring systemic-to–pulmonary artery shunt. Larger, prospective studies should be conducted to confirm these findings.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution.

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