Cardiology in the Young

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High acetylsalicylic acid dosing in infants after modified Blalock–Taussig shunt

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Abstract

Objective: Shunt-related adverse events are frequent in infants after modified Blalock–Taussig despite use of acetylsalicylic acid prophylaxis. A higher incidence of acetylsalicylic acid-resistance and sub-therapeutic acetylsalicylic acid levels has been reported in infants. We evaluated whether using high-dose acetylsalicylic acid can decrease shunt-related adverse events in infants after modified Blalock–Taussig. *Methods:* In this single-centre retrospective cohort study, we included infants ⩽1-year-old who underwent modified Blalock–Taussig placement and received acetylsalicylic acid in the ICU. We defined acetylsalicylic acid treatment groups as standard dose (⩽7 mg/kg/day) and high dose (⩾8 mg/kg/day) based on the initiating dose. *Results:* There were 34 infants in each group. Both groups were similar in age, gender, cardiac defect type, ICU length of stay, and time interval to second stage or definitive repair. Shunt interventions (18 versus 32%, $p = 0.16$), shunt thrombosis (14 versus 17%, $p = 0.74$), and mortality (9 versus 12%, $p = 0.65$) were not significantly different between groups. On multiple logistic regression analysis, single-ventricle morphology (odds ratio 5.2, 95% confidence interval of 1.2–23, $p = 0.03$) and post-operative red blood cells transfusion ⩾ 24 hours [odds ratio 15, confidence interval of (3–71), $p < 0.01$] were associated with shunt-related adverse events. High-dose acetylsalicylic acid treatment [odds ratio 2.6, confidence interval of (0.7–10), $p = 0.16$] was not associated with decrease in these events. *Conclusions:* High-dose acetylsalicylic acid may not be sufficient in reducing shunt-related adverse events in infants after modified Blalock–Taussig. Post-operative red blood cells transfusion may be a modifiable risk factor for these events. A randomised trial is needed to determine appropriate acetylsalicylic acid dosing in infants with modified Blalock–Taussig.

A modified Blalock–Taussig shunt is a surgically created systemic to pulmonary artery connection for neonates and infants with CHD who are in need of a durable and regulated source of pulmonary blood flow. This interposing shunt conduit has to remain patent for up to 4–6 months until the infant is old enough to undergo a primary repair or second-stage palliation. Inter-stage mortality following modified Blalock–Taussig shunt remains high (5–19%) despite aggressive post-operative surveillance and anti-coagulation management.[1–3] Risk factors leading to death in these patients are not well defined, though shunt thrombosis is considered one of the major contributing factors.

Placement of modified Blalock–Taussig shunt leads to an acute branching angle between the innominate artery and modified Blalock–Taussig shunt that creates shear patterns in the blood flow and platelet activation.[4] Modified Blalock–Taussig shunts are made of an artificially expanded polytetrafluoroethylene material that lacks an endothelial lining, thus triggering direct thrombin generation and thrombin-mediated platelet aggregation upon contact with blood.[5] In addition, neonates have an under-developed haemostatic system including coagulation protein, anti-fibrinolytic pathway, and platelet function, which may predispose them to bleeding and/or thrombotic events.[6,7]

Currently, unfractionated heparin infusion in the immediate post-operative period (24–72 hours) with concomitant anti-platelet therapy, primarily with acetylsalicylic acid, is used to reduce the risk of shunt thrombosis.[8,9] Although low-dose acetylsalicylic acid has been shown to reduce shunt thrombosis and mortality in infants with modified Blalock–Taussig shunt,[10] these rates still remain high and are thought to be related to a high incidence of acetylsalicylic acid resistance (up to 80%) in this population.[11–13] Furthermore, in neonates with good

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response to acetylsalicylic acid, the anti-platelet effect is inadequate up to 24–48 hours after administration of acetylsalicylic acid, the period during which most of the thrombotic events occur.[8,12] Administration of a higher dose of acetylsalicylic acid has been shown to overcome acetylsalicylic acid resistance in few adult and paediatric studies.[11,14,15]

In our centre, we implemented a pragmatic high-dose acetylsalicylic acid protocol to minimise adverse events in infants after modified Blalock-Taussig shunt in July 2013. In this retrospective study, we evaluated the inter-stage effectiveness of high-dose acetylsalicylic acid protocol in reducing shunt-related events compared to standard-dose acetylsalicylic acid following modified Blalock–Taussig shunt. We hypothesised that high-dose acetylsalicylic acid would reduce shunt-related adverse events after modified Blalock–Taussig shunt placement. Furthermore, determination of factors associated with post-operative risk of increased shunt-related events was done.

Materials and methods

After approval from the Institutional Review Board of the University of Tennessee Health Science Center, data were collected retrospectively from a chart review of infants aged ⩽1-year-old who underwent modified Blalock–Taussig shunt palliation from 1 January, 2009, to 31 July, 2017, at Le Bonheur Children's Hospital. We excluded patients from final analysis if the patient had known thrombophilia or congenital platelet disorder or required extracorporeal life support in the operating room or within 4 hours on arrival to cardiac ICU after modified Blalock–Taussig shunt placement. We implemented the high-dose acetylsalicylic acid protocol in July 2013. The American College of Chest Physicians has established the "standard" paediatric dose of 1–5 mg/kg of acetylsalicylic acid for neonates and infants requiring a modified Blalock–Taussig shunt palliation.[16] We defined high dose as twice the upper standard dose. High-dose acetylsalicylic acid therapy was defined as ⩾8 mg/kg/day and standard dose as ⩽7 mg/kg/day.

Shunt thrombosis was defined as worsening cyanosis and absence of shunt murmur with supportive evidence of partial or complete thrombosis on Doppler echocardiography, conventional angiography, or CT angiography, post-surgical or post-mortem findings, or urgent shunt-related intervention or replacement was performed.

Data collection and management

Data were collected for each patient from the electronic health record, including demographics, cardiac defect, duration of cardiopulmonary bypass if performed, laboratory data, shunt-related interventions or procedures, Doppler echocardiography, angiography, CT angiography, timing and amount of aspirin dosing, timing, duration, and dose of unfractionated heparin, use of other anti-thrombotic medications, amount and timing of blood products transfused, length of mechanical ventilator support, length of stay in ICU, 30-day mortality, inter-stage mortality, and bleeding complications defined as documented gastrointestinal haemorrhage, intracranial haemorrhage, or pulmonary haemorrhage requiring more than 20 cc/kg of red blood cells or platelet transfusion, and cessation of acetylsalicylic acid.

Primary outcome measures were incidence of partial or complete shunt thrombosis, incidence of shunt-related intervention, and inter-stage mortality. Shunt-related adverse events were defined as a composite outcome measure if the patient had inter-stage mortality, shunt thrombosis, or shunt-related intervention before the primary repair, or second-stage palliation.

Statistical analysis

We compared categorical and continuous variables between standard- and high-dose acetylsalicylic acid groups using the χ^2-test, Fisher's exact test, or the Wilcoxon rank-sum test as applicable. To determine the risk factors for shunt thrombosis or shunt-related adverse events, simple logistic regression was performed between those with shunt thrombosis/shunt-related adverse events and without shunt thrombosis/shunt-related adverse events. To establish the final logistic regression model, we performed the backward model selection procedure including main effects of variables with the p-value <0.25 and keeping high-dose aspirin variable in the model. Odds ratios and 95% confidence intervals were calculated using the final multiple logistic regression model. A p-value of <0.05 was considered significant. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, United States of America).

Results

A total of 70 infants underwent modified Blalock–Taussig shunt placement during the study period. Among them, two patients who required extracorporeal life support post-operatively and did not receive acetylsalicylic acid were excluded from the final analyses. The underlying cardiac defects requiring modified Blalock–Taussig shunt included tetralogy of Fallot with pulmonary stenosis/atresia 21(28%), pulmonary atresia with intact ventricular septum 14(21%), tricuspid atresia 11(16%), hypoplastic left heart syndrome ± heterotaxy 8(12%), complex double-outlet right ventricle 5(7%), unbalance atrioventricular canal defect 4 (6%), and others 5(7%). On the basis of pre-defined acetylsalicylic acid dosing criteria, we identified 34 patients in each group. Though high-dose acetylsalicylic acid protocol was applied since July 2013, we found three patients that received high-dose acetylsalicylic acid before July 2013 and three patients who received standard-dose acetylsalicylic acid after the protocol implementation.

Comparison of demographic, clinical, and laboratory variables

Both groups were similar in demographic and clinical characteristics except increased use of cardiopulmonary bypass –32% in high-dose versus 6% in standard-dose acetylsalicylic acid ($p = 0.01$) – and distribution of operating surgeons among groups –84% in high-dose versus 65% in standard-dose acetylsalicylic acid by surgeon 1 ($p = 0.005$), as shown in Table 1. Similarly, when comparing peri-operative laboratory values, both groups were similar with exception of lower median pre-operative platelet count (207×10^9/L versus 268×10^9/L, $p = 0.03$) and higher median post-operative white cell count (12.5×10^6/L versus 9×10^6/L, $p = 0.007$) in high-dose versus standard-dose acetylsalicylic acid group, as shown Table 2.

Acetylsalicylic acid dosing, use of other anti-thrombotic agents, and blood product transfusion

High-dose acetylsalicylic acid group had higher median (interquartile range) dose of acetylsalicylic acid at initiation

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Table 1. Comparison of demographic and clinical characteristics between standard- and high-acetylsalicylic acid dosing groups.

Variable	Standard-dose ASA n = 34	High-dose ASA n = 34	p-value
Demographic			
Age in months	0.46 (0.13–1.7)	0.16 (0.09–0.39)	0.07
Weight in kg	3.35 (2.9–4.1)	3.05 (2.6–3.6)	0.21
Female gender	12 (35%)	14 (41%)	0.62
Clinical			
SV cardiac morphology	11 (32%)	12 (35%)	0.74
CPB	2 (6%)	11 (32%)	0.01*
Surgeon			
1	22 (65%)	28 (82%)	
2	8 (24%)	1 (3%)	
3	1(3%)	5 (15%)	0.005*
4	3 (8%)	0	
Shunt size in mm			
⩽3.0	0	3 (9%)	0.08
3.5	15 (44%)	19 (56%)	
4.0	18 (53%)	11 (32%)	
>4.0	1 (3%)	1 (3%)	
First or second stage surgery	28 (82%)	25 (74%)	0.32
Age at second stage or definite repair in months	5.35 (3.96–7.53)	5.17 (3.87–6.37)	0.57
Time to second stage or definite repair in days	131 (105–198)	149 (117–172)	0.69
Duration of MV	3(1–6)	3 (1–6)	0.81
LOS in cardiac ICU	15.5 (8–52)	19 (8–37)	0.88
Shunt interventions	6 (18%)	11 (32%)	0.16
Shunt thrombosis	5 (15%)	6 (18%)	0.74
Inter-stage mortality	3 (9%)	4 (12%)	0.65
Composite outcome	11(32%)	11 (32%)	1
Bleeding complications	2 (6%)	3 (9%)	0.64

ASA = acetylsalicylic acid; CPB = cardiopulmonary bypass; MV = mechanical ventilation; SV = single ventricle; LOS = length of stay
*p value < 0.05 was considered significant.

[10.6 mg/kg/day (9–11.5) versus 6 (5–6.75), p = 0.0001], 1–2 months [9.5 (8–11.25) versus 5.8 (5–6.5), p = 0.0001], 2–4 months [8 (6.75–9.5) versus 5.3 (4.3–6.3), p = 0.0001], and 4–6 months [7 (6–8) versus 5.6 (3.75–6.5), p = 0.008] period compared to standard-dose acetylsalicylic acid (Figs 1a–d). Use of other anti-thrombotic agents including unfractionated heparin infusion in the immediate post-operative period, low molecular heparin, and clopidogrel was similar in both groups. However, the duration of unfractionated heparin infusion was longer (3 days versus 2 days, p = 0.008) in the standard-dose acetylsalicylic acid group (Table 3). There was more frequent use of red blood cells transfusion in the standard-dose acetylsalicylic acid group during the intraoperative (56 versus 24%, p = 0.006) and ⩾24 hours post-operative period (53 versus 24%, p = 0.04) compared to the high-dose acetylsalicylic acid group (Table 3).

Comparison of primary and secondary outcomes

There was no difference in the incidence of shunt thrombosis, shunt-related intervention, inter-stage mortality, and shunt-related adverse events between groups (Table 1). Overall, the median (interquartile range) duration for shunt thrombosis was 21 (2–102) days and the median time to death was 56 (15–135) days after modified Blalock–Taussig shunt with a mortality rate of 10%. The 30-day mortality was 2.8%. Also, the bleeding complication rate of 6% in the standard-dose versus 9% high-dose acetylsalicylic acid group (p = 0.64) was similar.

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Risk factors for shunt-related adverse events

Infants with (n = 22) and without (n = 46) shunt-related events were similar in age, weight, gender, cardiac defect, cardiopulmonary bypass use, peri-operative haemoglobin level, white cell count and platelet count, and time to primary repair or second-stage palliation. Infants with shunt-related events, however, had longer duration of mechanical ventilation [median (interquartile range) 3 days (1–4) versus 5.5(1–23), p = 0.02] and length of stay in ICU [median (interquartile range) 14.5 days (7–25) versus 35.5 (11–56), p = 0.02]. Also, a higher proportion of infants with shunt-related events received red blood cells transfusion ⩾ 24 hours post-operatively (64 versus 30%, p = 0.017) compared to infants without shunt-related events. On simple logistic regression analysis, duration of mechanical ventilation support and red blood cells transfusion ⩾ 24 hours post-operatively was associated with shunt-related adverse events (Table 4). Furthermore, on multiple logistic regression analysis, as illustrated in Figure 2, single-ventricle cardiac defect with odds ratio of 5.2 at confidence interval of 1.2–23.4 (p = 0.03) and red blood cells transfusion ⩾ 24 hours post-operatively with odds ratio 14.9 at confidence interval of 3.12–71 (p = 0.0007) were associated with shunt-related adverse events. High-dose acetylsalicylic acid with odds ratio of 2.6 at confidence interval of 0.68–9.9 (p = 0.16) (Fig 2) was not associated with decreased shunt-related adverse events on multi-variate regression analysis.

Risk factors for shunt thrombosis included length of stay in ICU and red blood cells transfusion ⩾ 24 hours post-operatively (Table 5). However, on multiple logistic regression analysis only red blood cells transfusion ⩾ 24 hours post-operatively with odds ratio of 16 at 95% confidence interval of 2.54–100.5 (p = 0.003) was associated with shunt thrombosis. High-dose acetylsalicylic acid was not associated with decrease in shunt thrombosis with odds ratio of 3.69 at confidence interval of 0.75–18.17 (p = 0.11).

Table 2. Comparison of peri-operative laboratory variables between standard- and high-dose acetylsalicylic acid groups.

Variable	Standard-dose ASA	High-dose ASA	p-value
Pre-operative			
Haemoglobin in g/dL	15.6 (13.1–15.4)	14.9 (13.5–17.3)	0.84
WBC count × 10^6/L	11.3 (9.7–14.8)	11.4 (7.1–15.2)	0.97
Platelet count × 10^9/L	268 (167–398)	207 (135–257)	0.03*
BUN in mg/dL	10 (5–14)	8 (5–10)	0.05
Creatinine in mg/dL	0.52 (0.26–0.66)	0.5 (0.4–0.63)	0.47
Post-operative			
Haemoglobin in g/dL	14.95 (13.7–16.6)	16.45 (13.6–17.7)	0.18
WBC count × 10^6/L	9 (7.6–12.7)	12.5 (10.3–17.7)	0.007*
Platelet count × 10^9/L	193 (126–246)	161 (125–225)	0.45
BUN in mg/dL	9 (6–12)	7.5 (5–13)	0.72
Creatinine in mg/dL	0.44 (0.29–0.59)	0.55 (0.4–0.7)	0.05

ASA = acetylsalicylic acid; BUN = blood urea nitrogen; WBC = white blood cell
*p value < 0.05 was considered significant.

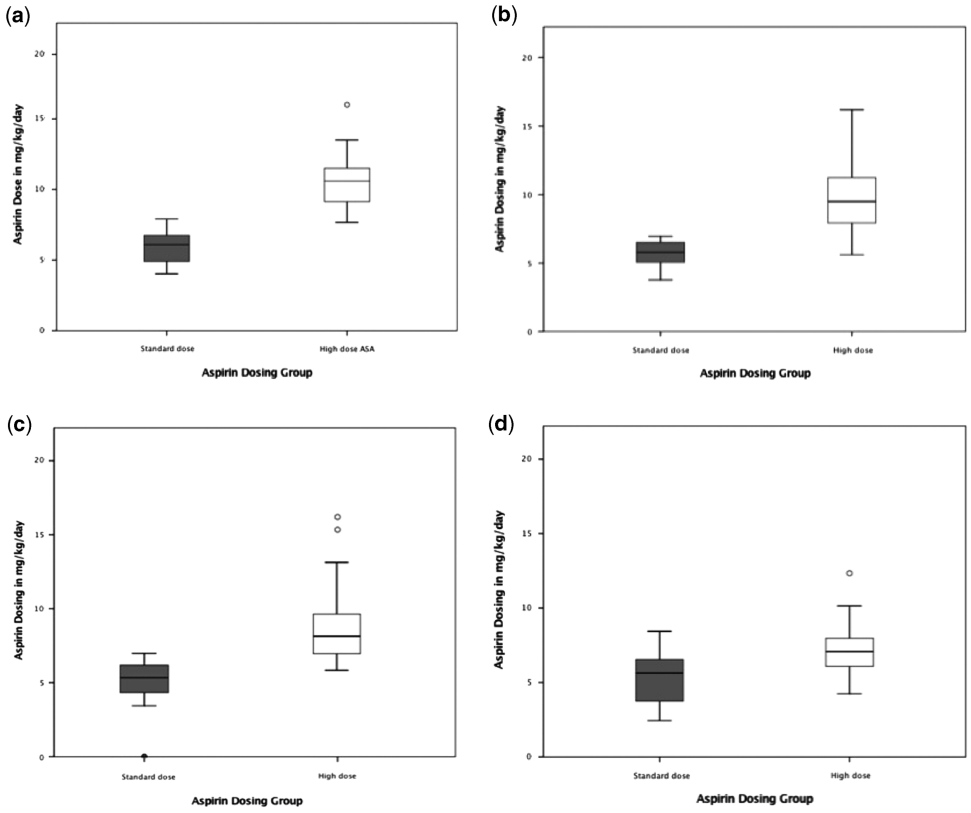

Figure 1. Comparison of prescribed acetylsalicylic acid dose between standard- and high- acetylsalicylic acid dosing groups. (A) Starting dose of acetylsalicylic acid postoperatively, (B) Postoperative acetylsalicylic acid dosing from 1 to 2-month period, (C) Postoperative acetylsalicylic acid dosing from 2 to 4-month period and (D) Postoperative acetylsalicylic acid dosing from 4 to 6-month period. p value was < 0.01* for all the comparisons.

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Table 3. Comparison of other antithrombotic agents and blood products utilisation between standard- and high- acetylsalicylic acid dosing groups.

Variable	Standard-dose ASA	High-dose ASA	p-value
Unfractionated heparin	31 (94%)	33 (97%)	0.61
UFH at unit/kg/hour	10 (10)	10 (10)	0.1
Duration of UFH in days	3 (2–4)	2 (1–3)	0.008*
LMWH	3 (9%)	1 (3%)	0.61
Clopidogrel	1 (3%)	6 (18%)	0.1
Pre-operative			
RBC	9 (26%)	7 (21%)	0.58
Plasma	2 (6%)	0	–
Platelets	1 (3%)	0	–
Intraoperative			
RBC	19 (56%)	8 (24%)	0.006*
Plasma	1 (6%)	3 (9%)	–
Platelets	0	0	–
Post-operative <24 hours			
RBC	11 (32%)	10 (29%)	0.8
Plasma	10 (29%)	9 (26%)	0.67
Platelets	0		
Post-operative ⩾24 hours			
RBC	20 (53%)	8 (24%)	0.04*
Plasma	1 (3%)	4 (12%)	–
Platelets	3 (9%)	2 (6%)	

ASA = acetylsalicylic acid; UFH = unfractionated heparin; LMWH = low molecular weight heparin; RBC = red blood cells transfusion
*p value < 0.05 was considered significant.

Red blood cells transfusion ⩾ 24 hours post-operatively was only risk factor associated with shunt-related intervention on simple logistic regression analysis (Supplementary Table S1). On multiple logistic regression analysis, single-ventricle lesion type with odds ratio of 4.64 at confidence interval of 1.15–18.64 (p = 0.03), red blood cells transfusion ⩾ 24 hours post-operatively with odds ratio of 9.68 at 95% confidence interval of 2.13–43.41 (p = 0.003), and high-dose acetylsalicylic acid with odds ratio of 4.61 at confidence interval of 1.12–18.9 (p = 0.04) were associated with shunt-related intervention. No variable was associated with mortality on simple logistic regression, but the power of this analysis was limited. The odds ratio of the selected variables, such as single-ventricle lesion type with odds ratio of 1.1 at confidence interval of 0.19–6.55 (p = 0.91), red blood cells transfusion ⩾ 24 hours post-operatively with odds ratio of 3.21 at 95% confidence interval of 0.60–17.23 (p = 0.17), and high-dose acetylsalicylic acid with odds ratio of 1.92 at confidence interval of 0.36–10.19 (p = 0.44) were not associated with mortality.

The median (interquartile range) pre-transfusion haematocrit was 38.1% (36.2–40) before red blood cells transfusion ⩾ 24 hours post-operatively in patients without shunt thrombosis in comparison to those with shunt thrombosis [35.5% (34.2–36.7), p = 0.036]. There was no significant difference in the median post-transfusion haematocrits between patients without shunt thrombosis [51% (49.1–52.0] compared to those without [52.3% (43.8–55.0), p = 0.522]. However, the median delta change in haematocrit percentage post-transfusion [14.8% (12.5–19.0)] was trended higher among those with shunt thrombosis compared to those without shunt thrombosis [12.5% (9.4–14.6), p = 0.076]. Also, the timing of transfusion in relation to modified Blalock–Taussig shunt placement was the median post-operative 18 days (3.75–46.5) in patients with shunt thrombosis compared to those without [3 days (2.5–5.0), p = 0.026].

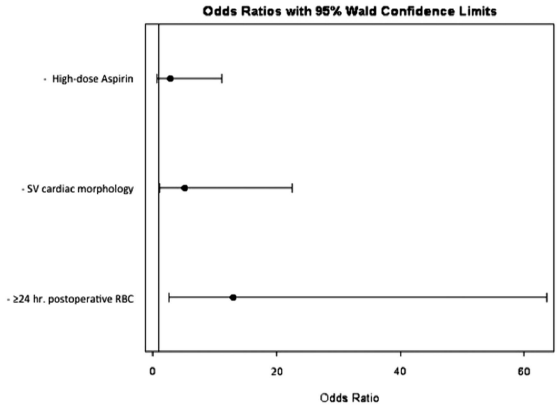

Figure 2. Risk factors associated with shunt-related adverse event on the final multiple logistics regression model. Single ventricular cardiac morphology (OR = 5.2, (95% CI 1.2–23.4), p = 0.03) and RBC transfusion ≥ 24 hours postoperatively (OR = 14.9, (95% CI 3.12–71, p = 0.0007) were associated with shunt-related adverse events, not high-dose aspirin (OR = 2.6 (95% CI 0.68–9.9), p = 0.16). *p < 0.05 was considered significant; [1]Single ventricle; [2]RBC-Red blood cells transfusion. p value was < 0.01* for all the comparisons.

Discussion

This is the first study to report the clinical effectiveness of a high-dose acetylsalicylic acid anti-thrombotic prophylaxis protocol in infants with modified Blalock–Taussig shunt placement. We found high-dose acetylsalicylic acid is not superior to standard-dose acetylsalicylic acid for anti-thrombotic prophylaxis in infants with modified Blalock–Taussig shunt placement within our cohort. Furthermore, post-operative red blood cells transfusion, a potentially modifiable risk factor, was associated with both shunt thrombosis and shunt-related adverse events.

Acetylsalicylic acid is often used as a sole agent to provide anti-thrombotic prophylaxis in infants with modified Blalock–Taussig shunt.[1,9] However, in a single-centre study, only 13% of infants with single-ventricle lesions palliated with modified Blalock–Taussig shunt or Sano shunt had >50% inhibition on arachidonic acid receptors on thromboelastography-platelet mapping using acetylsalicylic acid doses of 1–5 mg/kg/day.[13] Furthermore, about 38% of these patients had persistently inadequate inhibition of arachidonic acid receptors (<50% inhibition) after the third acetylsalicylic acid dose post-operatively.[13] In a similar study, only 20% of infants with single-ventricle lesions palliated with modified Blalock–Taussig shunt or Sano shunt had >50% inhibition of arachidonic acid receptors with acetylsalicylic acid dosing of 5–6 mg/kg/day. These patients with acetylsalicylic acid resistance did not respond to increasing acetylsalicylic acid dose to 8–10 mg/kg/day on the fifth post-operative day.[8] On the contrary, in a single-centre study of children undergoing high-risk cardiac procedures including modified

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Table 4. Simple logistic regression analysis to determine variables associated with shunt-related adverse events.

Variable	Odds ratio (OR)	95% confidence interval (CI)	p-value
Age	1.03	0.96–1.0	0.41
Weight	1.05	0.83–1.32	0.67
Female gender	0.67	0.28–1.94	0.45
SV cardiac morphology	1.96	0.67–5.75	0.22
CPB used	0.57	0.14–2.31	0.43
Surgeon one	1.33	0.41- 4.39	0.63
Shunt size $\leqslant$ 3.5 mm	1.32	0.47–3.70	0.59
Time to repair in days	1.00	0.99–1.01	0.40
Duration of MV	1.10	1.02–1.18	0.02*
LOS in cardiac ICU	1.01	0.99–1.03	0.18
Pre-operative			
Haemoglobin in g/dL	1.01	0.84–1.21	0.92
WBC count $\times 10^6$/L	0.99	0.89–1.10	0.82
Platelet count $\times 10^9$/L	1.00	0.99–1.01	0.24
BUN in mg/dL	1.02	0.94–1.10	0.72
Creatinine in mg/dL	2.63	0.27–25.9	0.41
Post-operative			
Haemoglobin in g/dL	1.03	0.87–1.22	0.75
WBC count $\times 10^6$/L	0.99	0.88–1.23	0.93
Platelet count $\times 10^9$/L	0.99	0.88–1.01	0.54
BUN in mg/dL	0.98	0.90–1.67	0.67
Creatinine in mg/dL	5.46	0.32–82	0.22
Duration of UFH in days	1.01	0.82–1.23	0.97
Pre-operative RBCTx	0.63	0.18–2.24	0.47
Intraoperative RBCTx	1.08	0.38–3.00	0.89
Post-operative <24 hours RBCTx	0.7	0.23–2.15	0.54
Post-operative $\geqslant$ 24 hours RBCTx	5.4	1.80–16.4	0.003*
High-dose acetylsalicylic acid	1.0	0.36–2.76	0.97

BUN = blood urea nitrogen; CPB = cardiopulmonary bypass; LOS = length of stay; MV = mechanical ventilation; RBCTx = red blood cells transfusion; SV = single ventricle; UFH = unfractionated heparin; WBC = white blood cell
*p value < 0.05 was considered significant.

Blalock–Taussig shunt, a decrease in acetylsalicylic acid resistance was observed with high-dose acetylsalicylic acid.[11]

Our study raises a provocative question as to whether acetylsalicylic acid alone even at high dose is optimum anti-thrombotic prophylaxis for infants with modified Blalock–Taussig shunt. There are many postulated mechanisms of acetylsalicylic acid resistance in these patients, including immature coagulation systems and platelets, poor acetylsalicylic acid absorption due to compromised cardiac output, inflammation related to cardio-pulmonary bypass, and persistent thrombin-mediated platelet activation on the non-endothelialised shunt surface.[3,4,17–20] As such acetylsalicylic acid alone may not be able to overcome the many thrombotic pathways, particularly in the immediate post-operative period. As seen in our study, the majority of shunt-related events occurred 72 hours post-operatively with a median time of occurrence of 21 (2–102) days, which is similar to other reports.[1–3]

In our cohort, we found that red blood cells transfusion $\geqslant$ 24 hours post-operatively and single-ventricle cardiac defects were associated with increased shunt-related adverse events. This observation is consistent with previously reported studies.[17,18,21,22] Single-ventricle lesions cause persistent hypoxia and low cardiac output, leading to low-grade inflammation, hepatic dysfunction, abnormal flow dynamics, endothelial and platelet activation, and increase in erythropoietin release and haemoglobin concentration.[23–25] All of these factors are postulated to

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Table 5. Simple logistic regression analysis to determine variables associated with shunt thrombosis.

Variable	Odds ratio (OR)	95% Confidence interval (CI)	p value
Age	0.05	0.001–2.7	0.14
Weight	0.90	0.59–1.38	0.64
Female gender	0.91	0.24–3.46	0.89
SV cardiac morphology	0.81	0.19–3.4	0.77
CPB use	0.93	0.18–4.92	0.93
Surgeon one	0.52	0.16–1.71	0.28
Shunt size $\leqslant$ 3.5 mm	1.21	0.34–4.29	0.76
Time to repair in days	1.00	0.99–1.01	0.54
Duration of MV	1.02	0.96–1.08	0.56
LOS in cardiac ICU	1.02	0.99–1.03	0.05
Pre-operative			
Haemoglobin in g/dL	0.92	0.71–1.18	0.49
WBC count $\times 10^6$/L	0.99	0.87–1.14	0.94
Platelet count $\times 10^9$/L	0.99	0.98–1.00	0.09
BUN in mg/dL	1.00	0.90–1.11	0.97
Creatinine in mg/dL	3.47	0.21–56.7	0.38
Post-operative			
Haemoglobin in g/dL	1.00	0.82–1.24	0.96
WBC count $\times 10^6$/L	1.004	0.86–1.18	0.96
Platelet count $\times 10^9$/L	0.99	0.98–1.00	0.15
BUN in mg/dL	0.95	0.83–1.08	0.46
Creatinine in mg/dL	2.91	0.10–79	0.52
Duration of UFH in days	1.01	0.79–1.28	0.94
Pre-operative RBCTx	1.27	0.29–5.45	0.75
Intraoperative RBCTx	0.85	0.22–3.21	0.80
Post-operative <24 hours RBCTx	0.41	0.08–2.09	0.28
Post-operative $\geqslant$ 24 hours RBCTx	9.00	1.77–45.85	0.008*
High-dose acetylsalicylic acid	1.24	0.34–4.54	0.74

BUN = blood urea nitrogen; CPB = cardiopulmonary bypass; LOS = length of stay; MV = mechanical ventilation; RBCTx = red blood cells transfusion; SV = single ventricle; UFH = unfractionated heparin; WBC = white blood cell
*p value < 0.05 was considered significant.

increase the risk of thrombotic events in infants with single-ventricle physiology.

The significant association of post-operative red blood cells transfusion with shunt thrombosis is a very important one. Post-operative red blood cells transfusion is a potentially modifiable risk factor. Red blood cells are often transfused to increase haemoglobin concentration above the normal range to enhance oxygen delivery in these patients. Currently, transfusion thresholds in this population are not well defined but can range between the haematocrit values of 35–45.[26,27] In our cohort, the median pre-transfusion was 35.5% in patients with shunt thrombosis with trend towards higher delta change in haematocrit percent after transfusion. Also, in our cohort the median post-transfusion haematocrit was about 51–52%. Anderson et al reported a median initial post-operative haematocrit of 41% and for every five additional percentage points of haematocrit, an infant's odds of early shunt occlusion more than doubled (odds ratio, 2.70; p = 0.009).[28] Sahoo et al showed that haemodilution to a haematocrit of 45% can improve shunt patency in the immediate post-operative period.[29] In a study assessing in-hospital modified Blalock–Taussig shunt thrombosis, post-operative red blood cells transfusion trended to be higher in infants with shunt thrombosis.[2]

Adverse effects of red blood cells transfusion are not trivial; they can increase blood viscosity, promote thrombin generation by tissue factor bearing microparticles, worsen immune

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dysregulation, and alter haemodynamic profile due to microcirculation derangements.[27] Most studies assessing risks and benefits of red blood cells transfusion are limited to the perioperative period in infants with CHDs.[26,30–32] The most emerging data suggest that a restrictive red blood cells strategy is equally effective in comparison to liberal red blood cells transfusion in children with CHD.[26]

There are several limitations to this study. The study analyses were exploratory and are only hypotheses generating. Additional prospective data analyses are warranted for further validation of the study results. The high-dose acetylsalicylic acid protocol was implemented clinically without planned evaluation of the protocol compliance and assessment of platelet function. Therefore, we were unable to assess whether high-dose acetylsalicylic acid achieved a significant change in platelet function compared to standard acetylsalicylic acid dose. Also, the patients in the standard acetylsalicylic acid group were from a different time period, which can lead to differences in other aspects of clinical practice between two groups. Five patients in the high-dose acetylsalicylic acid group also received clopidogrel in comparison with one patient in the standard-dose acetylsalicylic acid group. We were unable to account for clopidogrel as a confounder because of small sample size. We were unable to assess if a temporal relationship occurs between the timing of red blood cells transfusion and the shunt-related events.

Despite these limitations, our study provides important information on limited efficacy of a pragmatic high-dose acetylsalicylic acid protocol for inter-stage anti-thrombotic prophylaxis in infants with modified Blalock–Taussig shunt. This has helped us to implement an algorithm based on qualitative platelet function testing to better guide acetylsalicylic acid dosing. Functional platelet testing is now performed on day 1 post-surgery and after three doses in our centre. In our opinion, assessment of clot formation potential by applying more physiological whole-blood qualitative platelet function assays – viscoelastic assays and impedance aggregometry – may be needed to better guide various anti-thrombotic prophylaxis strategies. We also identified postoperative red blood cells transfusion as a potentially modifiable risk factor to decrease shunt thrombosis and shunt-related intervention in this population. There is a need to evaluate the current practice to better ascertain the risks and benefits of postoperative red blood cells transfusion in this population.

Conclusions

High-dose acetylsalicylic acid may not improve anti-thrombotic prophylaxis in infants with modified Blalock–Taussig shunt. Postoperative red blood cells transfusion may be a modifiable risk factor to reduce shunt-related adverse events. Randomised controlled trials are needed to determine appropriate dosing of acetylsalicylic acid and red blood cell transfusion thresholds in infants with modified Blalock–Taussig shunt.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951118002536

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Conflicts of Interest. None declared.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of relevant guidelines on human experimentation (USA) and with the Helsinki Declaration of 1975, as revised in 2008, and had been approved by the Institutional Committee of the University of Tennessee Health Science Center, Memphis, USA.

References

1. Ahmad U, Fatimi SH, Naqvi I, et al. Modified Blalock–Taussig shunt: immediate and short-term follow-up results in neonates. Heart Lung Circ 2008; 17: 54–58.
2. Guzzetta NA, Foster GS, Mruthinti N, Kilgore PD, Miller BE, Kanter KR. In-hospital shunt occlusion in infants undergoing a modified Blalock–Taussig shunt. Ann Thorac Surg 2013; 96: 176–182.
3. Gedicke M, Morgan G, Parry A, Martin R, Tulloh R. Risk factors for acute shunt blockage in children after modified Blalock–Taussig shunt operations. Heart Vessels 2010; 25: 405–409.
4. Celestin C, Guillot M, Ross-Ascuitto N, Ascuitto R. Computational fluid dynamics characterization of blood flow in central aorta to pulmonary artery connections: importance of shunt angulation as a determinant of shear stress-induced thrombosis. Pediatr Cardiol. 2015; 36: 600–615.
5. Adipurnama I, Yang MC, Ciach T, Butruk-Raszeja B. Surface modification and endothelialization of polyurethane for vascular tissue engineering applications: a review. Biomater Sci 2016; 5: 22–37.
6. Toulon P, Berruyer M, Brionne-Francois M, et al. Age dependency for coagulation parameters in paediatric populations. Results of a multicentre study aimed at defining the age-specific reference ranges. Thromb Haemost 2016; 116: 9–16.
7. Del Vecchio A, Motta M, Romagnoli C. Neonatal platelet function. Clin Perinatol 2015; 42: 625–638.
8. Mir A, Frank S, Journeycake J, et al. Aspirin resistance in single-ventricle physiology: aspirin prophylaxis is not adequate to inhibit platelets in the immediate postoperative period. Ann Thorac Surg 2015; 99: 2158–2164.
9. Agarwal A, Firdouse M, Brar N, et al. Incidence and management of thrombotic and thromboembolic complications following the Norwood procedure: a systematic review. Clin Appl Thromb/Hemost: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis 2017; 23: 911–921.
10. Li JS, Yow E, Berezny KY, et al. Clinical outcomes of palliative surgery including a systemic-to-pulmonary artery shunt in infants with cyanotic congenital heart disease: does aspirin make a difference? Circulation 2007; 116: 293–297.
11. Emani S, Trainor B, Zurakowski D, et al. Aspirin unresponsiveness predicts thrombosis in high-risk pediatric patients after cardiac surgery. J Thorac Cardiovasc Surg 2014; 148: 810–814; discussion 4-6.
12. Heistein LC, Scott WA, Zellers TM, et al. Aspirin resistance in children with heart disease at risk for thromboembolism: prevalence and possible mechanisms. Pediatr Cardiol 2008; 29: 285–291.
13. Truong DT, Johnson JT, Bailly DK, et al. Platelet inhibition in shunted infants on aspirin at short and midterm follow-up. Pediatr Cardiol 2017; 38: 401–409.
14. Lev EI, Solodky A, Harel N, et al. Treatment of aspirin-resistant patients with omega-3 fatty acids versus aspirin dose escalation. J Am Coll Cardiol 2010; 55: 114–121.
15. Gurbel PA, Bliden KP, DiChiara J, et al. Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect (ASPECT) study. Circulation 2007; 115: 3156–3164.
16. Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (Suppl 2): e737S–e801S.
17. Cholette JM, Rubenstein JS, Alfieris GM, et al. Elevated risk of thrombosis in neonates undergoing initial palliative cardiac surgery. Ann Thorac Surg 2007; 84: 1320–1325.
18. Fenton KN, Siewers RD, Rebovich B, Pigula FA. Interim mortality in infants with systemic-to-pulmonary artery shunts. Ann Thorac Surg 2003; 76: 152–156; discussion 6-7.

19. Rajasekhar D, Kestin AS, Bednarek FJ, Ellis PA, Barnard MR, Michelson AD. Neonatal platelets are less reactive than adult platelets to physiological agonists in whole blood. Thromb Haemost 1994; 72: 957–963.
20. Straub A, Smolich J, d'Udekem Y, Brizard C, Peter K, Horton S. Activation of platelets in young infants during cardiopulmonary bypass. Thromb Haemost 2010; 103: 466–469.
21. Manlhiot C, Brandao LR, Kwok J, et al. Thrombotic complications and thromboprophylaxis across all three stages of single ventricle heart palliation. J Pediatr 2012; 161: 513–519 e3.
22. Todd Tzanetos DR, Yu C, Hernanz-Schulman M, Barr FE, Brown NJ. Prospective study of the incidence and predictors of thrombus in children undergoing palliative surgery for single ventricle physiology. Intensive Care Med 2012; 38: 105–112.
23. Redford DT, Paidy SR, Steinbrenner EB, Nielsen VG. Effects of profound hypoxemia on coagulation & fibrinolysis in normal individuals. Blood Coagul Fibrinolysis: An International Journal in Haemostasis and Thrombosis 2016; 27: 228–231.
24. Mace S, Borkat G, Liebman J. Hepatic dysfunction and cardiovascular abnormalities. Occurrence in infants, children, and young adults. Am J Dis Child 1985; 139: 60–65.
25. Haga P, Cotes PM, Till JA, Minty BD, Shinebourne EA. Serum immunoreactive erythropoietin in children with cyanotic and acyanotic congenital heart disease. Blood. 1987; 70: 822–826.
26. Cholette JM, Swartz MF, Rubenstein J, et al. Outcomes using a conservative versus liberal red blood cell transfusion strategy in infants requiring cardiac operation. Ann Thorac Surg 2017; 103: 206–214.
27. Garcia-Roa M, Del Carmen Vicente-Ayuso M, Bobes AM, et al. Red blood cell storage time and transfusion: current practice, concerns and future perspectives. Blood Transfus. 2017; 15: 222–231.
28. Anderson BR, Blancha VL, Duchon JM, et al. The effects of postoperative hematocrit on shunt occlusion for neonates undergoing single ventricle palliation. J Thorac Cardiovasc Surg 2017; 153: 947–955.
29. Sahoo TK, Chauhan S, Sahu M, Bisoi A, Kiran U. Effects of hemodilution on outcome after modified Blalock-Taussig shunt operation in children with cyanotic congenital heart disease. J Cardiothorac Vasc Anesth 2007; 21: 179–183.
30. Manlhiot C, McCrindle BW, Menjak IB, et al. Longer blood storage is associated with suboptimal outcomes in high-risk pediatric cardiac surgery. Ann Thorac Surg 2012; 93: 1563–1569.
31. Howard-Quijano K, Schwarzenberger JC, Scovotti JC, et al. Increased red blood cell transfusions are associated with worsening outcomes in pediatric heart transplant patients. Anesth Analg 2013; 116: 1295–1308.
32. Dasgupta R, Parsons A, McClelland S, et al. Association of haematocrit and red blood cell transfusion with outcomes in infants with shunt-dependent pulmonary blood flow and univentricular physiology. Blood Transfus 2015; 13: 417–422.

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