Heparin Response in Patients Undergoing Arterial Switch Operations

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ABSTRACT

Introduction/Study Questions

We aim to determine the incidence of abnormal heparin response in a neonatal population undergoing the arterial switch operation (ASO), and to determine if abnormal heparin response is associated with increased post-bypass transfusion requirements or thrombotic complications.

Methods

We performed a retrospective analysis of all patients with D-TGA presenting for ASO at our institution from Jan. 2012 to Sept. 2017. Demographics, baseline coagulation profile, heparin dosing and blood product administration were collected from the EPIC EMR. We defined abnormal heparin response as requiring a second dose of heparin. We used STATA for all analysis, with Wilcoxon rank-sum test for continuous variables, and chi-squared test for nominal data.

Results

79 patients fit inclusion. 24% (19 of 79) of patients had an abnormal response to heparin. No differences in demographic characteristics were noted. Only baseline ACT was noted to differ between groups, 154s [143-162 s] versus 147s [131-154], p = 0.03), with those in the "Abnormal Response" group having a lower baseline ACT. There were no other differences in baseline coagulation studies. We did not find any difference in post-operative transfusion requirements between two groups. 4 patients had postoperative thrombotic complications, all in the normal response group.

Discussion

We found that at our institution the incidence of abnormal heparin response in neonates undergoing arterial switch operation is slightly higher than those reported in the literature. The known ATIII deficiency and immature coagulation system in neonates would support our finding. An interesting trend we have noticed in our patient population is the increased incidence of abnormal heparin response in the past two years, possibly due to changes in formulation. In our cohort, the transfusion requirements, chest tube outputs, and the incidence of thrombotic complications were not influenced by the patients responsiveness to heparin pre-bypass.

BACKGROUND

Initiation of cardiopulmonary bypass (CPB) requires anticoagulation. Heparin is the most accepted anticoagulant used in adult and pediatric cardiac surgery. Heparin binds to, and increases the activity of, antithrombin III (ATIII). Some patients mount an abnormal heparin response leading to suboptimal anticoagulation with standard doses used for CPB. The quoted incidence of heparin resistance in adults is up to 22%, with some evidence linking heparin resistance to death. Few studies have examined the incidence of abnormal heparin response in the pediatric population. And despite the fact that neonates possess decreased levels of ATIII, still less is known about neonatal heparin resistance.

We thus aim to determine the incidence of abnormal heparin response in a neonatal population undergoing the arterial switch operation (ASO), and determine if abnormal heparin response is associated with post-bypass coagulopathy and/or thromboembolic complications.

METHODS

With Institutional Review Board approval, we performed a retrospective analysis of all patients with D-TGA presenting for ASO at our institution from Jan. 2012 to Sept. 2017.

Exclusion Criteria:

- aortic arch reconstruction
- palliative arterial switch procedures.

We defined abnormal heparin response as one requiring a second pre-bypass dose of heparin after the initial bolus of our standard dose of 400 IU/kg. Institutionally, we require a minimum ACT of 380 seconds for initiation of CPB.

We collected:

- demographics,
- baseline coagulation profile
- heparin doses and ACT levels,
- blood product administration using EPIC electronic medical record.

We used STATA for all analysis, with Wilcoxon rank-sum test for continuous variables, and chi-squared test for nominal data.

RESULTS

79 patient met inclusion criteria:

- 60 (76%) patients exhibited normal response to heparin
- 19 (24%) patients exhibited an abnormal response to heparin

Table 1. Baseline Characteristics

Characteristic	Normal (n= 60)	Resistant (n= 19)	P-value
Age (days)	7.5 [6-11]	7 [6-15]	0.48
Weight (kg)	3.43 [3.00-3.70]	3.3 [2.88-3.85]	0.49
Female	16 (27%)	8 (42%)	0.20
Male	44 (73%)	11 (58%)	0.20
Hemoglobin (g/dL)	13.4 [12.5-15.2]	14 [12.8-15.7]	0.24
Platelets (x10^3/uL)	287 [218-391]	277 [232-350]	0.91
INR	1.2 [1.1-1.3]	1.1 [1-1.2]	0.17
PT (s)	14.6 [13.7-15.5]	14.5 [13.9-15.3]	0.71
PTT (s)	36.4 [33.1-40.2]	37.3 [34.7-41]	0.83
Fibrinogen (mg/dL)	260 [212-314]	303 [203-343]	0.37
Baseline ACT (s)	154 [143-162]	147 [131-154]	0.03

Table 2. Transfusion Requirements and Chest Tube Outputs

Outcome Variable	Control (n= 60)	Resistant (n= 19)	P-value
Intra-op pRBC (mL/kg)	2.17 [0-7.91]	0 [0-6.35]	0.51
ICU pRBC (mL/kg)	0 [0-5.51]	0 [0-5.12]	0.25
Platelets (mL/kg)	11.53 [6.45-19.35]	12.35 [8.70-15.36]	0.85
Cryoprecipitate (mL/kg)	3.55 [0-6.69]	5.88 [3.03-7.14]	0.25
Chest tube output/kg/24 hours	5.26 [3.93-8.17]	6.07 [4.29-13.25]	0.25

RESULTS

Table 3. Factor Concentrate Requirements

Factors	Control	Resistant	Total
Did Not Receive	42 (70%)	11 (58%)	53
Received	18 (30%)	8 (42%)	26
Total	60	19	79

p = 0.31

Thrombotic Complications:

- 6 patients had thrombotic complications
- 2 patients had thrombosis prior to presenting to the operating room
- None of the patients who had thrombotic complications demonstrated heparin resistance

DISCUSSION

The incidence of abnormal heparin response in patients with D-TGA undergoing ASO is 24%. This is slightly higher than the rate quoted in literature. However, the incidence of heparin resistance has increased significantly after 2015, with a rate of 60% in 2017. This could be due to changes in formulation and bioavailability.

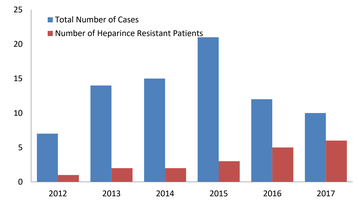

Figure 1. Heparin Resistance Distribution by Year

There was a statistically significant difference between the baseline ACT between the two groups. However, this is not clinically significant. There were no differences in the transfusion requirements, chest tube outputs, or the incidence of requiring factor concentrates.

Thrombotic complications were not observed in the heparin resistant group; however, the sample size limits the significance of this finding.

CONCLUSIONS

The rate of heparin resistance in patients with D-TGA undergoing arterial switch operations is 24% in our population. There were no differences in baseline demographics, or coagulation profile amongst the patients who were resistant versus those who were not resistant. There were also no differences in the incidence and amount of transfusion of blood products or post-operative thrombotic complications between the two groups.

Additional prospective studies, and studies examining larger cohorts, could elucidate the true incidence of heparin resistance; and alternative coagulation studies, such as ROTEM or TEG, could better characterize the baseline coagulation function of neonates undergoing cardiovascular surgery.

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