Variability of antithrombotic use in patients with hypoplastic left heart syndrome and its variants following first and second stage palliation surgery: A national report using the National Pediatric Cardiology Quality Improvement Collaborative registry

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Abstract

Purpose: Patients with hypoplastic left heart syndrome (HLHS) and its variants following palliation surgery are at risk for thrombosis. This study examines variability of antithrombotic practice, the incidence of interstage shunt thrombosis and other adverse events following Stage I and Stage II palliation within the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) registry.

Methods: This was a multi-center retrospective review using the NPC-QIC registry including patients from 2008-2013 across 52 surgical sites. Antithrombotic medications used at Stage I and Stage II discharge were evaluated. Variability of antithrombotic use at the individual patient level and intersite variability, incidence of shunt thrombosis and other adverse events such as cardiac arrest, seizure, stroke and need for cardiac catheterization intervention in the interstage period were identified. Antithrombotic strategy of hybrid Stage I patients was evaluated but they were excluded from variability and outcomes analysis.

Results: 932 Stage I and 923 Stage II patients were included in the study; 93.8% of Stage I were discharged on aspirin and 4% were discharged on no antithrombotic; 77% of Stage II were discharged on aspirin and 17.5% were discharged on no antithrombotic. Three patients (0.2%) presented with interstage shunt thrombosis. The majority of patients who died during interstage or required shunt dilation and/or stenting were discharged home on aspirin.

Conclusion: Aspirin is the most commonly used antithrombotic following Stage I and Stage II palliation. There is more variability of antithrombotic choice following Stage II compared to Stage I. The incidence of interstage shunt thrombosis and associated adverse events were rare.

Introduction

Hypoplastic left heart syndrome remains one of the most complex and challenging of congenital heart diseases. A three stage surgical palliation has become the standard of care for these patients. Stage I palliation consists of the standard Norwood procedure combined with a Blalock-Taussig (BT) shunt, right ventricular to pulmonary artery (RV to PA) conduit or central shunt.[1] Of late, the hybrid procedure has emerged as an alternative to the standard stage I palliative procedures and includes placement of pulmonary artery bands and a ductus arteriosus stent.[1 2] This is followed by Stage II palliation comprising of a superior-cavopulmonary anastomosis and then the final stage of palliation comprising of a Fontan procedure. Patients who have undergone the hybrid procedure undergo a comprehensive stage II procedure comprising of removal of the PA bands with possible PA reconstruction, removal of the PDA stent with aortic arch reconstruction, a Damus–Kaye–Stansel connection of the aortic and PA roots, a bidirectional superior cavopulmonary connection, and an atrial septectomy.[2]

Despite advances in surgical techniques and peri-operative monitoring, the early mortality rate for these patients remain high, ranging from 4 to15%.[3 4] The national mortality rate for patients undergoing the Norwood operation is 1 in 5 patients and this varies based on center and surgical volume.[5-10] The time between discharge from the hospital following Stage I palliation and presentation for Stage II palliation (also referred to as the interstage period), poses risk due to hemodynamic instability with high mortality rates attributed to several factors. These include low birth weight, genetic syndromes, greater than moderate ventricular dysfunction, greater than moderate atrioventricular valve regurgitation, restrictive or intact atrial septum, recoarctation of the aortic arch, obstruction of pulmonary arteries or the shunt, delayed age at surgery, longer cardiopulmonary bypass times and postoperative renal dysfunction.[4 6]

One of the potentially fatal complications following Stage I palliation is thrombosis of the systemic to pulmonary shunt.[11-13] The nature of the Stage I surgery, small infant size, shunt size as well as abnormalities of the coagulation cascade and platelet function due to cardiopulmonary bypass places these patients at risk for shunt thrombosis.[14-19] BT shunt thrombotic occlusion rates ranging from 1-17% have been noted in previous studies.[11 20 21] The occlusion can occur during the immediate post-operative period as well during the interstage period . The use of routine thromboprophylaxis has been advocated but there is still a lack of conclusive evidence about its risk versus benefits.[14 22 23]

The purpose of our study was to evaluate variability in antithrombotic practices at discharge following Stage I and Stage II surgery. The secondary aim of our study was to assess the incidence of interstage shunt thrombosis and other thrombosis related morbidity and mortality such as seizures, stroke, cardiac arrest and need for cardiac catheterization during interstage in relation to discharge antithrombotic treatment.

Materials and Methods

This was a multicenter retrospective chart review using the NPC-QIC registry database**.** The NPC-QIC Improvement Collaborative registry is a secure, web-based system (REDCap, Vanderbilt University) with data voluntarily entered by participating centers in the United States.[24] Patient enrollment in the database was started in June 2008. Local IRB approval was obtained prior to extracting data from the registry. Any infant with HLHS or other complex single ventricle malformation that underwent Stage I (Norwood or Norwood-variant) procedure and who was discharged alive is eligible for enrollment in the registry. This registry captures data on patient demographics, clinical presentation, hospitalization, Stage I procedure, initial

hospital discharge, interstage clinic visits and hospitalization episodes. All patients who underwent standard Stage I palliation who survived to hospital discharge from 2008-2013 were included in this analysis. The thromboprophylaxis strategy of patients undergoing the hybrid procedure was evaluated, but given that they may be exposed to perioperative stresses different from that of Norwood / Norwood variant (which are performed on cardiopulmonary bypass), they were excluded from Stage I site variability and outcomes analysis. All Stage II patients were included in the analysis irrespective of the type of Stage I palliation procedure they received (Norwood versus the hybrid procedure). Data elements such as type of discharge anti-coagulants and adverse events applicable for that clinical time period were analyzed.

A descriptive review of the choice of antithrombotic medication at the time of Stage I and Stage II following discharge was performed. Variation in practice patterns at individual patient level as well as among various surgical sites was assessed. In order to evaluate interstage adverse outcomes, information about documented shunt thrombosis or catheter-based shunt intervention and other potentially related thrombotic adverse outcomes associated with thromboprophylaxis use such as stroke, seizures and cardiac arrest were collected.

Results

Patient population

A total of 932 standard Stage I patients were included in the study. This group was predominantly males (62%) and Caucasian (74%) with HLHS being the most common diagnosis (68%) (Table 1). The majority (56%) of these patients underwent a Norwood procedure with RV to PA conduit with 41% undergoing Norwood procedure with BT shunt. The remaining 3% of patients received central shunts or RV to PA conduits but were classified as “other”. Of the 932

patients discharged from Stage I, 69 (7.4%) died and 17 (1.8%) required transplant. A total of 86 patients underwent hybrid Stage I palliation and were excluded from Stage I analysis. The Stage II study population included 923 patients with a predominantly male (63%) Caucasian (76%) population and the most common diagnosis being HLHS (67%) (Table 1). Surgical centers with >10 patient enrollment in the NPC-QIC database were included during assessment of inter-site variability. Centers with <10 patient enrollment were excluded from intersite variability analysis. Figure 1 shows the distribution of centers according to the center's surgical volume. The surgical center numbers were maintained the same in all figures. *Interstage Antithrombotic use*

The antithrombotic medications were classified into the following groups: aspirin only, enoxaparin only, clopidogrel only, warfarin only, combination therapy (aspirin + at least one of the other drugs) and no antithrombotic. Although the mechanisms of action for these medications are different, for ease of reading, all of the above medications will be referred to as "discharge antithrombotic or antithrombotic regimen" from this point onwards.

Stage I discharge regimen: Aspirin was the most frequently used anti-thrombotic and was also the most frequently used solitary drug of choice in 87% of total patients (Table 2). Approximately 7% of the patients were discharged on a multidrug antithrombotic regimen consisting of aspirin with or without clopidogrel and/ or warfarin and/ or enoxaparin. Hence approximately 93.8% of patients were discharged on aspirin either as single or part of multidrug regimen. Four percent of the patients were sent home with no antithrombotic. Aspirin was the most common discharge anti-coagulant irrespective of whether the patient had a RV to PA conduit (88%) or a BT shunt (86%) placed.

Hybrid discharge regimen: There were a total of 86 hybrid patients discharged who were included in the registry. 75 of the 86 (87%) went home on aspirin only, 6 (7%) went home on no antithrombotic, 3 (3%) went home on enoxaparin and 2 (2%) went home on a combination medications.

Stage II discharge regimen:

There was more variability of discharge antithrombotic in the Stage II patients. Of the 923 Stage II patients 77 % of the patients were sent home on aspirin either as single or part of multidrug regimen (Table 2). Stage II patients were discharged home more frequently without any thromboprophylaxis when compared to the Stage I population (17.5% in Stage II versus 4% in Stage I). Patients went home more frequently on enoxaparin (4.7% in Stage II compared to 1.6% in Stage I). Four percent of the patients went home on multidrug regimen.

A separate analysis of the hybrid patients following comprehensive stage II was also performed. There were a total of 64 hybrids patients identified after Stage II and it was noted that a larger proportion of these patients (22 of 64 or 34.4%) were discharged on enoxaparin when compared to the non hybrid / standard patients (21 or 2.5%). 31% (20/64) were discharged on aspirin and almost 20% (13 of 64) went home without thromboprophylaxis.

Intersite variability*:* Inter-site variability on the choice of antithrombotic following standard Stage I and Stage II palliation is shown in Figures 2 and 3. Although the majority of the Stage I sites used aspirin as the choice of antithrombotic therapy at discharge, there were a few sites where up to 50% of the patients were discharged either on no antithrombotics or non-aspirin antithrombotic therapy. In addition, several sites discharged a significant number of their patients on combination medications. There was more intersite variability noted following Stage II

palliation as noted in Figure 3. Although aspirin was still the most frequently used medication at the time of discharge, there were sites where the vast majority of the patients were discharged on no antithrombotics and many sites where patients were discharged on enoxaparin or combination therapy.

Interstage Shunt thrombosis and other adverse outcomes

Interstage shunt thrombosis was identified in three patients (Table 3). All 3 patients underwent Stage I palliation with a BT shunt and were discharged on aspirin. Data is limited in terms of their clinical presentation but all 3 patients were readmitted with shunt thrombosis, which was confirmed by cardiac catheterization during that admission. The first patient was taken to surgery for central shunt placement with pulmonary artery augmentation. Ultimately the patient was not considered a satisfactory Stage II candidate and was withdrawn from the registry. The second patient had a stroke following shunt thrombosis and care was withdrawn. The third patient required ECMO and eventually underwent Stage II surgery.

Other adverse outcomes such as stroke, seizure and cardiac arrest were identified, and their discharge antithrombotic was evaluated (Table 3). A total of 11 patients were identified with cardiac arrest and 2 with stroke. All patients with cardiac arrest were discharged home on aspirin. Two patients had seizures of which one was sent home on aspirin and the other went home on no antithrombotic. Two patients suffered from stroke, the first discharged on clopidogrel and the other on enoxaparin.

Of the 69 patients who died during the interstage, 63 (91%) were discharged home on aspirin and the remaining 3 (4%) were on combination medications, 2 were on no antithrombotic (3%) and 1 was on enoxaparin (1.5%).

Interstage cardiac catheterization

A total of 44 patients (5% of total Stage I patients) were readmitted during the interstage period for BT shunt or RV to PA conduit dilation and /or stenting via cardiac catheterization. Thirty-seven of the 44 patients were sent home on aspirin at the time of Stage I discharge. This accounted for 4.5 % of the total patients (N=809) who went home on aspirin only (Table 4).

Discussion

Despite several advances in the management of single ventricle Norwood palliated patients, there continues to be significant morbidity and reported mortality rates. Thrombosis of the systemic to pulmonary artery shunt is one of the potentially life threatening complication in these patients following Stage I palliation. [3 4] Therefore maintaining patency of the BT shunt or the RV to PA conduit is of utmost importance. [11 18] The use of routine thromboprophylaxis has been advocated, but there is still lack of conclusive evidence regarding choice of medications, route, dosage and its impact on clinical outcomes. One of the largest prospective multicenter studiesfrom Fenton et al concluded that aspirin use decreased the risk of shunt thrombosis and its associated morbidity and mortality. [11] In the American Heart Association consensus statement for prevention and treatment of thrombosis in pediatric and congenital heart disease Giglia et al recommended long term use of low dose aspirin for prevention of long term thrombosis of systemic to pulmonary artery shunts in the absence of increased risk of bleeding (Class I; level of evidence B).[22] In 2013, Wessel et al found during a prospective randomized trial of Clopidogrel in infants with shunts that, 88% were being treated with aspirin.[23] Similar to the above studies, the vast majority of the Norwood centers in our cohort sent their patients home on antithrombotic therapy following Stage 1 palliation, with aspirin being the most common choice. Several centers also

used enoxaparin or clopidogrel, but infrequently or in combination with aspirin. Warfarin was never used as a solitary drug. Some patients were sent home on combination therapy (aspirin with at least one other drug). It is possible this may have been influenced by the post-operative or intensive care unit stay related complications such as line associated thrombosis (arterial or venous),stroke, or following interventional catheterization procedures (such a BT shunt stenting or balloon angioplasty) where there may be a desire for increased antithrombotic therapy. However we were unable to assess these factors due to unavailability of such data in the registry.

There was a relatively low rate of shunt related complications in this patient group during the interstage study period (<1%). This was lower compared to other studies where shunt occlusion rates in the immediate post-operative phase ranged from 4-15% [20 21] . We also suspect that the percentage of mortality that can be attributed to shunt thrombosis and its consequences may be underestimated since there is often a lack of histopathologic evidence for shunt thrombosis at the time of death due to lack of autopsies in all patient deaths.[11 25] Few studies have looked at advantages of one antithrombotic versus another in this population. It is likely that individual center and clinician practice drive some of the variation noted in this study. Variability in the hybrid patients may be accounted for by the difference in their mechanism of surgery as well as postoperative course compared to the Norwood population. Galantowicz et al in their study demonstrate a higher incidence of pulmonary embolism requiring anticoagulation with enoxaparin during the comprehensive Stage II postoperative period.[26] This may account for the larger proportion of patients who were discharged on lovenox following the comprehensive stage II palliation surgery.

Side effect profile, variable pharmacokinetic profile, requirement of expertise for close monitoring for drug levels for heparin and warfarin may also play an important role in the

decision making. It is also acknowledged that the optimal dose of aspirin has not been determined and pediatric patients have been shown to demonstrate aspirin resistance at doses currently being utilized[27]. Recent evidence for the optimal aspirin dosing and aspirin resistance is currently being evaluated with utilization of thromboelastography (TEG) with platelet mapping, aspirin resistance testing, and urine thromboxane levels.[28 29] It is interesting to note that all patients except one who suffered adverse outcomes from thrombosis were on antithrombotic at discharge. However information on dose of medication or compliance at home was not available through the database.

Limitations

This study is limited by its retrospective nature. The overall rate of shunt thrombosis and other morbidities were rare in the interstage period. Therefore it was not possible to identify a definite association with medical management choices. Lack of data on why medications were prescribed made it difficult to understand the reasoning behind therapeutic choices. Immediate postoperative Norwood associated shunt thrombosis and thrombotic complications are not reported in this database thereby limiting this descriptive review. Only 38 of the 69 patients who died had autopsies and therefore the total number of shunt thrombosis may have been an underestimate.

Conclusions

Aspirin is by far the most common choice for thromboprophylaxis following Stage I and Stage II palliation. Clopidogrel, enoxaparin and warfarin were also used, but infrequently or in addition to aspirin. Substantially more variation is noted in the type of discharge antithrombotic following

Stage II palliation with 17.5% of patients going home on no thromboprophylaxis compared to 4% after Stage I.

Despite this study having a large number of interstage patients, the incidence of adverse outcomes such as shunt thrombosis was rare. Given this low number, no significant association between shunt thrombosis and type of thromboprophylaxis could be derived. Other thrombotic complications such as seizures, stroke also occurred, with low frequency. Prospective studies, collaborations with more centers, other research registries, and individualized dosing studies or monitoring could prove to be beneficial in providing more insight.

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