Original Article

Appropriate Dose of Postoperative Intravenous Heparin Infusion in the Children undergoing Modified Blalock Taussig Shunt 4 mm and below in Size

Sanphasitvong V, MD[1], Tocharoenchok T, MD[1]

[1] Division of Cardio-Thoracic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Modified Blalock-Taussig shunt is the most common palliative systemic to pulmonary artery shunt performed in cyanotic congenital heart disease. Shunt thrombosis occurred in 1 to 17% of the operation that led to mortality. One major risk factor is a small shunt size under 4 mm. Systemic heparinization is a preventive measure for this subgroup with a cost of a bleeding complication. However, there is no standard dose for heparin infusion. The objective of this study is to determine the appropriate dose of heparin infusion to achieve APTT ratio of 1.5 to 2.

Materials and Methods: During 2007 to 2016, 220 patients who underwent off-pump modified Blalock-Taussig shunt of 4 mm and below in size at Siriraj Hospital were studied. After exclusion of the patients with pre-operative coagulopathy (APTT >30.5 sec), out of target APTT ratio and missing data, 60 patients were included. Demographic data, operative parameter, heparin infusion dosage, postoperative complications such as shunt thrombosis and postoperative bleeding were analyzed.

Results: Appropriate heparin infusion dose to achieve an APTT ratio of 1.5 to 2.0 was 18.27±8.84 unit/kg/hour. In the patient weight less than 2.5 kg, heparin infusion dose was 14.25±4.92 unit/kg/hour and never exceed 20 unit/kg/hour. Shunt thrombosis and bleeding complication were occurred in 11.7% and 8.3% of patients, respectively, without correlation to heparin dosage and time to achieve therapeutic APTT ratio.

Conclusion: To achieve an APTT ratio of 1.5 to 2, postoperative intravenous heparin infusion should be 18 unit/kg/hour. A smaller dose should be considered in low birth weight patients.

Keywords: Modified Blalock-Taussig shunt, Postoperative intravenous heparin infusion, Shunt thrombosis

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An aortopulmonary shunt is a palliative procedure in congenital heart disease. It is designed to increase pulmonary blood flow in cyanotic children with inadequate pulmonary blood flow. The Blalock-Taussig shunt was the first aortopulmonary shunt. It was performed in 1944 by Alfred Blalock of the John Hopkins University Medical Center[1]. The classic Blalock-Taussig shunt is a direct end to side anastomosis of the transected subclavian artery to the pulmonary artery. The classical shunt sacrifices the subclavian artery which can result in hand or arm ischemia. Short subclavian artery in some cases is also problematic in the classical shunt. The modified Blalock-Taussig shunt was introduced in 1976 by Gazzaniga using PTFE tube, avoiding sacrifice of the subclavian artery[2]. A major issue found after this operation is shunt thrombosis. The incidence reported ranges from 1 to 17%[3,4]. Risk factors of shunt thrombosis include patient age (<14 days), graft size (less than 4 mm), shunt on bypass, platelet use during operation[5].

Heparin infusion has been employed to reduce the incidence of shunt thrombosis[6-8], but no recommended dose was mentioned in the studies. In general the maintenance dose of heparin for infants is 10 to 25 unit/kg/hr[9]. However, there is no specific recommended dose of heparin infusion in the postoperative period. An appropriate dose of heparin is required to avoid both postoperative bleeding and shunt thrombosis, which usually occurs in the early postoperative period. At Siriraj Hospital, 1 mg/kg of heparin was loaded intra-operatively dose and protamine was not routinely given at the operative conclusion. In the postoperative period, Heparin was selectively infused in the patient who underwent modified Blalock-Taussig shunt placement with graft size of 4 mm and smaller. The APTT ratio target is 1.5 to 2.0. Heparin infusion was given vary in dose depending on an attending physician.

The objective of this study is to investigate the appropriate dose of heparin infusion to achieve the APTT ratio of 1.5 to 2 in infants who underwent modified Blalock Taussig shunt (MBTS) placement of 4 mm or smaller in size. The secondary objective is to analyze

Correspondence to:

Tocharoenchok T.

Division of Cardiothoracic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Phone: +66-2-4197998, **Fax:** +66-2-4126160

E-mail: tee03662@hotmail.com

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complications of heparin infusion such as bleeding, heparin induced thrombocytopenia (HIT), prolonged chest tube drainage.

Materials and Methods

Patient population

The present study was approved by the Institutional Review Board. We retrospectively reviewed patients who underwent modified Blalock Taussig shunt between 2007 to 2016. The inclusion criteria were patients using modified Blalock-Taussig shunt 4 mm and below without cardiopulmonary bypass support and receiving heparin infusion during the postoperative period. The exclusion criteria were patients with pre-operative coagulopathy (APTT >30.5 sec), out of target APTT ratio and missing data.

We used a pilot study to calculate the appropriated sample size. Sixty patients were included in this study as guided by sample size calculation.

MBTS was performed through a thoracotomy at the side opposite to the course of the aortic arch. A subclavian artery was used for the shunt inflow. Gore-Tex expanded polytetrafluoroethylene grafts (W.L. Gore & Assoc, Flagstaff, AZ, USA) were used as a shunt conduit in all patients. Shunt size was determined by patient size, size of the PA to be shunted and surgeon preference. The patent ductus arteriosus was routinely left open and prostaglandin infusion was discontinued at the time of clamps removal. Heparin was administered for 100 units/kg in all patients and was not reversed by protamine at the end of the procedure. If there was no evidence of bleeding in the intensive care unit, heparin infusion would be started. The heparin starting dose and measurement of an APTT ratio varied among physicians but the target APTT ratio was 1.5 to 2.0 for all patients. Therapeutic heparin level was the heparin infusion rate (unit/kg/h) that achieved a stable target APTT ratio (APTT ratio in the target range for 2 or more consecutive measurements. The present study was approved by the Siriraj Institutational Review Board (616/2560(EC4)).

Outcomes measurement

We retrieved clinical data from the electronic outpatient database, inpatient database, and follow-up records.

Pre-operative parameters, operative procedure details and post-operative outcomes were collected.

Statistical analysis

We used IBM SPSS statistics for Windows, version 20 (IBM Corp., Armonk, NY, USA) for the statistical analyses. Descriptive statistics were used to determine the baseline characteristics of the patients. Data are presented as medians with interquartile range, means with standard deviation or frequencies with percentages as appropriate. Univariate analysis for an association between each variable used the Chi-square or t-test/Mann-Whitney U test as appropriate. A p-value <0.05 was set as the threshold for statistical significance.

Results

Between January 2007 and December 2016, 220 patients underwent MBTS 4 mm or lower without cardiopulmonary bypass support. Details were illustrated in Figure 1. Due to missing data, out-of-target targeted APTT ratio and pre-operative coagulopathy, 160 patients were excluded from the analysis. Therefore, a total of 60 patients were included in the analysis. The most common diagnosis was univentricular heart disease, followed by pulmonary atresia with ventricular septal defect and tetralogy of Fallot (Table 1).

A median age and weight at time of operation were 24.5 days and 3,200 grams. There was equal distribution between male and female. Most of patients were term newborn (n = 48, 82.8%) (Table 2).

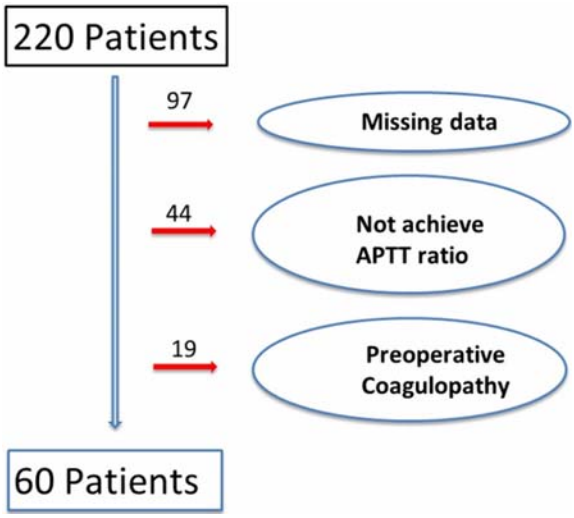

Figure 1. Study scheme.

Table 1. Diagnosis

Diagnosis	Total (n = 60)
UVH with PS/PA	23 (38.3%)
PA/VSD	12 (20%)
TOF	11 (18.3%)
PA/IVS	7 (11.7%)
DORV with PS/PA	4 (6.7%)
dTGA	2 (3.3%)
ccTGA with PS	1 (1.7%)

UVH with PS/PA = univentricular heart with pulmonary stenosis or atresia, PA/VSD = pulmonary atresia with ventricular septal defect, TOF = Tetralogy of Fallot, PA/IVS = pulmonary atresia with an intact ventricular septum, DORV with PS/PA = double outlet right ventricle with pulmonary stenosis or atresia, d-TGA = d-transposition of the great arteries, ccTGA with PS = corrected transposition of the great arteries with pulmonary stenosis

The mean shunt size was 3.58 mm and the mean operative time was 119 minutes. A median time to achieve targeted APTT ratio was 15 hours (Table 3). The mean initial heparin dose was 13.6 unit/kg/hour and the mean therapeutic heparin dose was 18.9 unit/kg/hour. We noticed that the patients with weight below 2.5 kg trend to have lower mean therapeutic heparin dose of 14.25 unit/kg/hour and in this group of patients, no one received heparin dose higher than 20 unit/kg/hour to achieve the targeted APTT ratio (Table 4).

Complications occurred in 22 patients (22%). Seven patients (11.7%) had shunt thrombosis. Five patients (8.3%) had postoperative bleeding that required reoperation to stop bleeding. Ten patients (16.6%) had new-onset thrombocytopenia (platelet count below 100,000/ml) and no patient had prolonged pleural drainage. Shunt thrombosis was not related to initial heparin infusion dose, therapeutic heparin infusion and time to achieve targeted APTT ratio as shown in Table 5. Bleeding required reoperation was not related to heparin infusion dose as shown in Table 6.

Discussion

Shunt thrombosis rate in our study was comparable to other studies (1 to 17%)[3,4], despite studying in a high-risk population (who have shunt size 4 mm and below) that may be affected by heparinization. However, our study showed a high rate of bleeding complication of more than 5% which could be due to heparin infusion. In our study, the heparin infusion dose was not related to both bleeding and shunt thrombosis complication, but our sample size calculation was designed to get appropriate heparin infusion dose rather than obtain risk factors for complications. So the firm conclusion could not be drawn for the relationship between those two factors.

The appropriate heparin infusion dose to achieve targeted APTT ratio in our study was 18.27 unit/kg/hour which stays in normal heparin infusion dose for infants[9]. However, in low birth weight patients (<2.5 kg), the appropriate infusion dose should be lower and should not be given exceed 20 unit/kg/hour. This effect may be caused by the immaturity of the homeostasis system and a subsequent low level of coagulation factors, resulted from under production.

Study limitations

Besides retrospective nature, some limitations existed in the present study. First, we had many missing APTT ratio data. Second, our patients varied in diagnosis and pre-operative comorbidity. Complex lesion and a sicker patient may affect heparin infusion dose, complications from surgery and complication from heparin infusion.

Conclusion

To achieve an APTT ratio of 1.5 to 2 in the children undergoing modified Blalock Taussig shunt 4 mm and below in size, postoperative intravenous heparin infusion should be at 18 unit/kg/hour. Fourteen unit/kg/hour doses should be considered in low birth weight patient and dose should not exceed 20 unit/kg/hour. Shunt thrombosis occurred in 7 patients (11.7%).

What is already known on this topic?

Shunt thrombosis after modified Blalock Taussig shunt operation is one of the most troublesome complications.

Table 2. Demographic data

	Total (n = 60)
Age, days	
Median (IQR)	24.5 (11, 70)
Sex	
Male	31 (51.7%)
Female	29 (48.3%)
Term/preterm	(n = 58)
Term	48 (82.8%)
Preterm	10 (17.2%)
Body weight, grams	
Median (IQR)	3,200 (2,781, 3,778)

Table 3. Operative data

	Total (n = 60)
Shunt size, mm	
Mean (SD)	3.58 (0.27)
Shunt size, n (%)	
3 mm	5 (8.3%)
3.5 mm	41 (68.3%)
4 mm	14 (23.3%)
Operative time, min	
Mean (SD)	118.73 (50.11)
Time to achieve therapeutic	(n = 55)
APTT ratio, hour	
Median (IQR)	15 (9.5, 29)

Table 4. Heparin dose

	Total, n = 60	BW <2.5 kg, n = 8	BW ≥2.5 kg, n = 52	*p*-value
Initial heparin dose (U/kg/hour)	n = 53	n = 5	n = 48	0.98
Mean (SD)	13.60 (5.41)	13.66 (5.83)	13.60 (5.43)	
Therapeutic heparin dose (U/kg/hour)				
Mean (SD)	18.27 (8.84)	14.25 (4.92)	18.89 (9.17)	0.17

Table 5. Shunt thrombosis

	Thrombosis, n = 7	No thrombosis, n = 53	*p*-value
Initial heparin dose (U/kg/hour)	n = 6	n = 47	
Mean (SD)	15.73 (8.14)	13.34 (5.02)	0.31
Therapeutic heparin dose (U/kg/hour)			
Mean (SD)	20.57 (9.73)	17.97 (8.77)	0.47
Time to achieve therapeutic APTT ratio, hour	n = 6	n = 49	
Median (IQR)	14 (9, 22.5)	16 (9.5, 28.5)	0.89

Table 6. Bleeding complication

	Bleeding, n = 5	No bleeding, n = 55	*p*-value
Initial heparin dose (U/kg/hour)	n = 5	n = 48	
Mean (SD)	12.12 (2.2)	13.76 (5.63)	0.23
Therapeutic heparin dose (U/kg/hour)			
Mean (SD)	15.02 (7.94)	18.57 (8.93)	0.40

Heparin infusion has been used to reduce this condition in high-risk patients. But heparin infusion has to be adjusted to balance between bleeding complication and the benefit in prevention of shunt thrombosis.

What this study adds?

Heparin infusion 18 unit/kg/hour is the recommended starting dose.

Potential conflicts of interest

The authors declare no conflicts of interest.

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ขนาดยาเฮพารินบริหารทางหลอดเลือดดำที่เหมาะสมในผู้ป่วยเด็กในช่วงหลังการผ่าตัดทำทางเชื่อมระหว่างหลอดเลือดแดงร่างกายกับหลอดเลือดแดงพัลโมนารีชนิดบลาล็อค-เทาวสิกดัดแปลงที่ใช้หลอดเลือดเทียมขนาด 4 มิลลิเมตรและต่ำกว่า

วุฒิพงศ์ สรรพสิทธิ์วงศ์, ธีรพงศ์ โตเจริญโชค

ภูมิหลัง: การผ่าตัดทำทางเชื่อมระหว่างหลอดเลือดแดงร่างกายกับหลอดเลือดแดงพัลโมนารี ชนิดบลาล็อค-เทาวสิกดัดแปลงเป็นการผ่าตัดบรรเทา อาการที่พบได้บ่อยที่สุดในเด็กโรคหัวใจพิการแต่กำเนิดชนิดเขียว การผ่าตัดชนิดนี้มีภาวะแทรกซ้อนที่พบได้บ่อยหลังผ่าตัดอย่างหนึ่งคือภาวะที่ทางเชื่อมเกิดอุดตัน ซึ่งพบได้ประมาณ 1 ถึง 17% โดยภาวะแทรกซ้อนนี้นำไปสู่การเสียชีวิตของคนไข้หลังผ่าตัด ปัจจัยเสี่ยงที่สำคัญอย่างหนึ่งในการเกิดทางเชื่อมอุดตันคือการผ่าตัดที่ใช้ทางเชื่อมขนาดเล็ก 4 มม. หรือเล็กกว่า มีการให้ยาเฮพารินซึ่งเป็นยาละลายลิ่มเลือดเพื่อป้องกันภาวะทางเชื่อมอุดตันในผู้ป่วยกลุ่มนี้ แต่ว่าการให้ยาละลายลิ่มเลือดในช่วงหลังผ่าตัด อาจทำให้คนไข้มีความเสี่ยงในการเกิดภาวะเลือดออกหลังผ่าตัดสูงขึ้น ดังนั้นการให้ยาละลายลิ่มเลือดในขนาดที่เหมาะสมจึงมีความสำคัญ เพื่อที่ยาจะสามารถป้องกันการเกิดภาวะทางเชื่อมอุดตันหลังผ่าตัดได้โดยไม่สูงเกินไปจนทำให้เกิดภาวะเลือดออกหลังผ่าตัด อย่างไรก็ตามในปัจจุบันยังไม่มีขนาดยาที่แนะนำในผู้ป่วยกลุ่มนี้เพื่อให้ได้ระดับ APTT ratio 1.5 ถึง 2.0 จุดประสงค์ของการวิจัยนี้เพื่อที่จะหาขยาดยาเฮพารินที่เหมาะสมในผู้ป่วยกลุ่มนี้เพื่อที่จะได้ APTT ratio ตามเป้าหมายและศึกษาภาวะแทรกซ้อนจากการบริหารยาเฮพารินในผู้ป่วยกลุ่มนี้

วัสดุและวิธีการ: ในช่วงปี พ.ศ. 2550 ถึง 2559 มีผู้ป่วยทั้งหมด 220 คน ได้รับการผ่าตัดทำทางเชื่อมระหว่างหลอดเลือดแดงร่างกายกับหลอดเลือดแดงพัลโมนารี ชนิดบลาล็อซ-เทาวสิกดัดแปลงในขนาด 4 มม. หรือเล็กกว่า โดยไม่ใช้เครื่องปอดหัวใจเทียมในโรงพยาบาลศิริราช หลังจากได้ตัดผู้ป่วยที่ระดับการแข็งตัวของเลือดผิดปรกติตั้งแต่ก่อนผ่าตัด (APTT ratio >30.5 วินาที) ผู้ป่วยที่ระดับ APTT ratio หลังผ่าตัดไม่อยู่ในช่วง 1.5 ถึง 2.0 และผู้ป่วยที่ข้อมูลสูญหาย มีผู้ป่วยทั้งหมด 60 รายที่อยู่ในการศึกษานี้ ข้อมูลทั่วไปของผู้ป่วย ข้อมูลในช่วงผ่าตัด ขนาดยาเฮพารินที่บริหารทางหลอดเลือดดำและข้อมูลภาวะแทรกซ้อนหลังผ่าตัด เช่น ภาวะทางเชื่อมอุดตันหลังผ่าตัดจากลิ่มเลือด ภาวะเลือดออกหลังผ่าตัด ถูกรวบรวมและนำมาวิเคราะห์

ผลการศึกษา: ขนาดยาเฮพารินบริหารทางหลอดเลือดดำที่ทำให้ระดับ APTT ratio อยู่ในช่วง 1.5 ถึง 2.0 คือ 18.27±8.84 u/kg/hour ในผู้ป่วยที่น้ำหนักตัวน้อยกว่า 2.5 กิโลกรัม ขนาดยาเฮพารินที่บริหารทางหลอดเลือดดำควรลดลงเป็น 14.25±4.92 u/kg/hour และไม่ควรให้เกิน 20 u/kg/hour. ภาวะทางเชื่อมอุดตันด้วยลิ่มเลือดหลังผ่าตัดและภาวะเลือดออกหลังผ่าตัดพบได้ 11.7% และ 8.3% ของผู้ป่วยตามลำดับ และไม่พบว่ามีความสัมพันธ์ของขนาดยาเฮพารินที่ให้และระยะเวลาในการที่ APTT ratio ถึงเป้าหมายต่อภาวะแทรกซ้อนทั้ง 2 ที่เกิดขึ้น

สรุป: เพื่อที่จะได้ระดับ APTT ratio 1.5 ถึง 2 ขนาดยาเฮพารินที่บริหารทางหลอดเลือดดำควรเป็น 18 u/kg/hour และขนาดยาเฮพารินที่ให้ในผู้ป่วยที่น้ำหนักตัวน้อยกว่า 2.5 กิโลกรัมควรจะลดลง