ARTIGO ORIGINAL ORIGINAL ARTICLE

PLATELET COUNT DROP AFTER RAPID DEPLOYMENT AORTIC VALVE IMPLANTATION

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Abstract

Background: *A transient postoperative drop in platelet count is an expected finding after aortic valve replacement using extracorporeal circulation. The implantation of the Perceval valve has been associated with a more intense drop of platelet count compared to other bio-prostheses. This study analyses and compares the platelets progression associated with the Perceval and Intuity valves.*

Methods: *The data was collected retrospectively for patients submitted to isolated aortic valve replacement with the Perceval valve (80 patients) and the Intuity valve (141 patients) in our institution between March 2014 and December 2018. The groups were further divided into those who receive platelet transfusion and those who did not.*

Results: *The minimum values of platelet count were 54% and 67% of the preoperative platelet count in the patients treated with a Perceval and an Intuity valves, respectively ($p<0.001$). In the patients transfused with platelets, the minimum values were 52% and 79% of the preoperative platelet count, respectively ($p<0.01$). Recovery of the count was faster in the patients treated with an Intuity valve. Abnormal bleeding and transfusion of packed red blood cells were not significantly different between groups (without platelet transfusion: $p=0.71$ and $p=0.99$, respectively; with platelet transfusion: $p=0.58$ and $p=0.99$, respectively).*

Conclusion: *Compared to the Intuity valve, the Perceval valve is associated with a transient, but significant, drop in platelet count. This drop was not associated to an increased risk of bleeding. Platelet transfusion, in this setting, should be judicious and not only ruled by absolute values.*

INTRODUCTION

The biologic rapid deployment valves were developed for aortic valve replacement surgery, as an alternative for high risk patients.[1] At the moment, two models are available on the market: Perceval S (Sorin Group Saluggia, Italy / Livanova, London, UK) and Intuity (Edwards Lifesciences, Irvine, California, USA). By allowing a faster implantation with minimal heart and aorta manipulation, they provide shorter operative times, reduced perioperative complications and better clinical outcomes maintaining excellent hemodynamic performances.[2,3,4]

A transient platelet drop is an expected postoperative finding. A reduction of 30-60% of the baseline values is common between the second and third days and is generally associated to the extracorporeal circulation.[5] A low count of platelets, particularly if severe, has the potential for bleeding complications, among others6. Additionally, the use of the Perceval valve has been associated with a more intense reduction and slower recovery of the platelet count and a higher need of packed red blood cells transfusion.[7,8]

The goals of this study were (1) to analyze the postoperative platelet response to Perceval and Intuity valves, (2) to compare the responses between the valves, and (3) identify associated adverse clinical events, such as bleeding.

PATIENTS AND METHODS

Population and study groups

A total of 224 consecutive patients underwent isolated Intuity or Perceval valve implantation, between March 2014 and December 2018, at our institution. The indication for surgery was the same as for conventional aortic valve replacement. The data from all the patients was retrospectively reviewed.

Multisystemic failure is a well-known factor of coagulation disturbance; for this reason, three patients were excluded due to rapid progressively multisystemic failure resulting in death.

To avoid the effect of platelet transfusion in the progression of the platelet levels, the patients that received platelet transfusion after surgery were analyzed separately. Therefore, four groups were established: (1) patients that received an Intuity valve and no postoperative platelet transfusion (IG, n=102); (2) patients that received a Perceval valve and no postoperative platelet transfusion (PG, n=60); (3) patients that received an Intuity valve and postoperative platelet transfusion (IpG, n=39); and (4) patients that received a Perceval valve and postoperative platelet transfusion (PpG, n=20).

Valve prostheses characteristics and implantation techniques

INTUITY[9]

The Intuity valve is a bioprosthesis with three bovine pericardial leaflets. Its design was based on the Magna Ease aortic bioprosthesis (Edwards Lifesciences, Irvine, California, USA) built on a covered expandable stainless-steel frame, at the bottom side of the valve. This cloth skirt is intended to expand in the left ventricular outflow tract subjacent to the native annulus; this way, it promotes stability and sealing between the aortic annulus and the frame and host tissue in-growth.

The anticalcification technology used is ThermaFix, a combination of both thermal and chemical agents developed to remove unstable glutaraldehyde residuals, the same used in other Edwards prostheses (such as Magna and Magna Ease).

After rinsing, the valve is connected to the specialized delivery system. Three guiding sutures, placed in the anulus at the nadir of each coronary cusps, pass though sewing ring in the valve and are used to align the valve with the annulus during the descent. Once in position, the three sutures are secured using tourniquets. The balloon is inflated to the appropriate pressure (varying according to the valve size). The delivery system is removed and the guiding sutures are tied.

PERCEVAL S[9]

The Perceval S valve is a bioprosthesis with three bovine pericardial leaflets mounted on a naked nitinol self-expandable frame; this frame is coated with Carbofilm™ to improve biocompatibility. Its design was based on the Freedom SOLO (Sorin Group Saluggia, Italy / Livanova, London, UK).

The anticalcification treatment is based on homocysteic acid, the same used in other Livanova prostheses (such as Pericarbon Freedom and Freedom SOLO).

The valve is compressed by a proper collapsing device and loaded onto the delivery device. No rinsing is required. Three guiding sutures help to align the valve with the annulus during the descent into subannular position. The valve then is released from the delivery device and balloon dilatation is performed at 4 atm of pressure for 30 seconds with continuous irrigation with sterile water at 37ºC. The guiding sutures are removed afterwards. The valve is kept in position by the stent against the intra-aortic wall.

Surgery and postoperative care

All patients were submitted to the same conventional surgical technique. The cardiopulmonary bypass was established with an arterial cannula in the ascending aorta, a double stage venous cannula through the right atrial appendage, and a left ventricle vent, placed through the right upper pulmonary vein. Cold blood cardioplegia was administered in an anterograde fashion. Complete decalcification of the aortic annulus was always performed. The choice of valve was made by the surgeon. At the end of the surgery, platelet and fresh plasma was administrated, if needed, according to clinical factors (such as, the amount of bleeding, the visual absence of clotting, and diffuse bleeding with no surgical explanation) and thromboelastography. Perioperative transesophageal echocardiogram was performed in all patients to confirm valve position, hemodynamics and to exclude paravalvular leaks.

Postoperative medication was the same for all patients, and started within 24h, according to the standard protocol of the department. It includes aspirin, statin, acetaminophen, metamizole, prophylactic enoxaparin, insulin (as needed), prophylactic cefazolin (or vancomycin if allergy), furosemide, pantoprazole, ondansetron (as needed), aminergic support (epinephrine, norepinephrine and/or dobutamine, as needed).

Platelet count measurements followed the standard routine of the department: within 24h previously to the surgery, within 1h after surgery; in the mornings of the following days; and at the 1-month follow-up visit.

Abnormal bleeding was defined as > 2ml/kg/h in first 2-3 hours, > 1ml/kg/h in the next 3 hours and/or > 0.5ml/kg/h in 12 hours. A thromboelastography was performed to guide the choice of products to transfuse. If the bleeding rate was worrisome and no clot was visible in the drainage, both platelets and fresh plasma were transfused before the thromboelastography results. If the bleeding rate was great and/or causing hemodynamic instability, a surgical exploration would be quickly performed.

Statistical analysis

Data collection and statistical analysis was carried out using SPSS v24. Continuous variables were treated as mean and standard deviation and compared with t-student tests, with a two-tailed distribution assuming unequal variances. Categorical variables were summarized as the number and/or percentage of subjects in each category and compared with Fisher's exact tests.

RESULTS

Patients that did not received postoperative platelet transfusion

The baseline characteristics for IG and PG are presented in Table 1. Overall, the two groups were not

Table 1 **Base characteristics.**

	No platelet transfusion			Platelet transfusion		
	Intuity (n=102)	Perceval (n=60)	*p*	Intuity (n=39)	Perceval (n=20)	*p*
Sex (female/male)	61/39 %	53/47 %	0.411	41/59 %	40/60 %	0.999
Age (years)	74.8 ± 5.6	76.6 ± 4.8	0.040	76.6 ± 6.7	77.7 ± 5.7	0.566
EuroScore II (%)	2.4 ± 1.4	2.5 ± 1.9	0.651	2.1 ± 1.2	2.8 ± 1.9	0.179
Arterial hypertension	94.1%	93.3%	0.999	92.3%	100%	0,544
Dyslipidemia	78.4%	76.7%	0.846	74.4%	75.0%	0,999
Impaired renal function[1]	78.4%	86.7%	0.216	82.1%	85.0%	0.999
Overweigh/obesity[2]	76.5%	80.0%	0.697	66.7%	75.0%	0.565
Coronary disease	36.3%	18.3%	0.020	43.6%	50.0%	0,784
Diabetes Mellitus	36.3%	43.3%	0.407	30.8%	35.0%	0,775
Insulin treated	2.9%	8.3%	0.148	0%	0%	
Atrial fibrillation3	18.6%	28.3%	0.173	15.4%	20.0%	0.721
Smoking history4	29.6%	26.7%	0.331	15.4%	20.0%	0.721
Thrombocytopenia5	7.8%	10.0%	0.773	30.8%	30%	0.999
Carotid disease	11.8%	8.3%	0.601	12,8%	5.0%	0,653
Pacemaker	4.9%	3.3%	0.999	5.1%	5%	0.999
Previous stroke or transient ischemic attack	3.9%	10.0%	0.175	7.7%	5%	0.999

Categorical variables are presented as percentage of subjects in each category and compared with t-student tests. Continuous variables were treated as mean and standard deviation and compared with Fisher's exact tests.
1 Impaired renal function was defined as glomerular filtration rate <80%.
2 Overweigh/obesity was defined as body mass index >25.
3 Any form: paroxysmal, persistent, permanent.
4 Former or active.
5 Thrombocytopenia was defined as a platelet level <150/ml.

different. The two exceptions were the higher mean age in the PG (a difference of 1.8 years, p=0.04) and the higher frequency of coronary disease in the IG (a difference of 18 percental points, p=0.02).

The differences in mean aorta cross clamping, extracorporeal circulation and operative times, between the groups, were, respectively, 1.5, 3.8 and 9.0 minutes, in favor of the IG (table 2). No relevant paravalvular leaks were found in any patients, in either group. Mean post implantation mean transvalvular gradient was 10.0 ± 3.7 mmHg with the Intuity valve and 8.9 ± 5.2 mmHg with the Perceval valve (p=0.458).

Platelet count progression for each group is presented in Image 1A. Preoperative means were 225 ± 68/ml in the IG and 217 ± 61/ml in the PG. In the first hour, there was a significant drop (p<0.001), in both groups, to about 70% of the preoperative count. In the following mornings, platelet count continued to decrease in the PG to a minimum of 53.8% (at the 3rd postoperative day). In the IG, after a small increase, the numbers dropped to a minimum of 67.2% of the preoperative count, 2 days after surgery. At the follow-up visit, the IG and PG presented a mean count of 123% and 98% of the preoperative count, respectively.

No statistically significant differences occurred between IG and PG regarding abnormal bleeding, bleeding related complications, in-hospital stay, major renal dysfunction, infection or death (see Table 2 for details).

A subanalysis excluding the patients with coronary disease was conducted. No relevant baseline differences were found. The differences in platelet progression remained similar. Abnormal bleeding occurred in 3.1% and 6.1% (p=0.65), in the patients implanted with an Intuity valve (n=65) and a Perceval valve (n=49), respectively; transfusion of packed red blood cells was performed in 9.2% and 12.2% (p=0.760) and transfusion of fresh plasma occurred in 7.7% and 2.0% (p=0.234), respectively. Major renal dysfunction was higher in the PG (10.0% vs 1.5%, p=0.083).

Patients that received postoperative platelet transfusion

The IpG received a mean of 1.38 units of platelets per patient and the PpG a mean of 1.45 units per patient, within the first day. No statistically significant differences were found in baseline characteristics and surgical outcomes (tables 1 and 2).

Table 2 **Surgical and post-operative outcomes.**

	No platelet transfusion			Platelet transfusion		
	Intuity (n=102)	Perceval (n=60)	*p*	Intuity (n=39)	Perceval (n=20)	*p*
Operatory times						
Aorta Clamping (minutes)	27.2 ± 6.8	28.7 ± 8.4	0.260	29.9 ± 12.0	26.6 ± 6.0	0,165
Cardiopulmonary bypass (minutes)	35.9 ± 8.7	39.7 ± 11.0	0.022	39.8 ± 16.4	36.2 ± 8.0	0,408
Operative time (minutes)	86.9 ± 20.3	95.9 ± 21.8	0.010	91.4 ± 26.8	91.2 ± 12.8	0,955
In-hospital stay						
ICU stay (days)	2.6 ± 1.5	2.7 ± 1.8	0.518	4.0 ± 3.2	4.0 ± 2.9	0.953
Hospital stay (days)	5.6 ± 2.8	6.3 ± 1.8	0.107	8.2 ± 5.7	7.9 ± 4.6	0.825
Post-operative complications						
Fresh plasma transfusion[1]	7.8%	1.7%	0.156	69.2%	40.0%	0.049
Red blood cell transfusion[1]	11.8%	11.7%	0.999	69.2%	70.0%	0.999
Abnormal bleeding[2]	3.9%	5.0%	0.711	64.1%	55.0%	0.578
Bleeding in the first 24h (ml)	466 ± 251	443 ± 363	0.635	1012 ± 466	1052 ± 757	0.829
Surgical exploration for bleeding	2.0%	0%	0.531	10.3%	5.0%	0.653
Significant renal dysfunction[3]	4.9%	8.3%	0.501	20.5%	15.0%	0.734
Renal replacement support[4]	1.0%	1.7%	0.999	2.6%	5.0%	0.999
Aminergic support5 >24h	19.6%	21.7%	0.840	38.5%	45%	0.780
Infection[6]	2.0%	5.0%	0.360	12.8%	15.0%	0.999

ICU - Intensive care unit.
Categorical variables are presented as percentage of subjects in each category and compared with t-student tests. Continuous variables were treated as mean and standard deviation and compared with Fisher's exact tests.
1 Transfusion of at least 1 unit.
2 Abnormal bleeding was defined as > 2ml/kg/h in first 2-3 hours, > 1ml/kg/h in the next 3 hours and/or > 0.5ml/kg/h in 12 hours.
3 Significant renal dysfunction was defined as KDIGO stages 2 and 3.
4 Renal replacement support was performed though Continuous Veno-Venous Hemodiafiltration.
5 Aminergic support was performed with at least one of the following: epinephrine, norepinephrine, dobutamine.
6 Respiratory, urinary and/or blood infection.

The platelet count progression for the IpG and the PpG is presented in image 1B. In the IpG, the count rose in the first morning, decreased in the second (to 79% of the preoperative count) and then increased gradually to 135% of the baseline levels, at the follow-up visit. In the PpG, the platelet levels were maintained in the first morning and then decreased gradually until the fourth morning (to 52% of the preoperative count); Afterwards, a slow recover occurred, with levels reaching 95% of the preoperative count at the follow-up visit. The differences between groups were statistically significant starting at the second morning.

DISCUSSION

As expected, regardless of the type of valve implanted, a platelet-count drop that reached a minimum between the second and third postoperative days, was observed. This drop was statistically significant when compared to the preoperative values. The preoperative and within 1-hour platelet count were very similar in both valves. After the first morning, and persisting at the follow-up visit (~1 month), the platelet count was higher in the IG: the lowest count was 67% and 54% of the preoperative count in the IG and the PG, respectively. Afterwards, the recovery was slower in the PG. The patients that received platelet transfusion had low baseline platelet count, but the overall progression and differences between valve groups was similar. Despite lower count in the groups that received Perceval valves (PG and PpG), bleeding and surgical exploration was not different between Perceval and Intuity groups. Platelet transfusion resulted in a significant increase in platelet count in the patients that receive an Intuity valve. This was not observed in the patients that received a Perceval valve. Higher bleeding in the PpG (5.0% vs 55.0% in PG, $p<0.001$) could result in platelet consumption and explain the "no increase" of platelets after transfusion, however, the IpG also had more bleeding than IG (3,9%

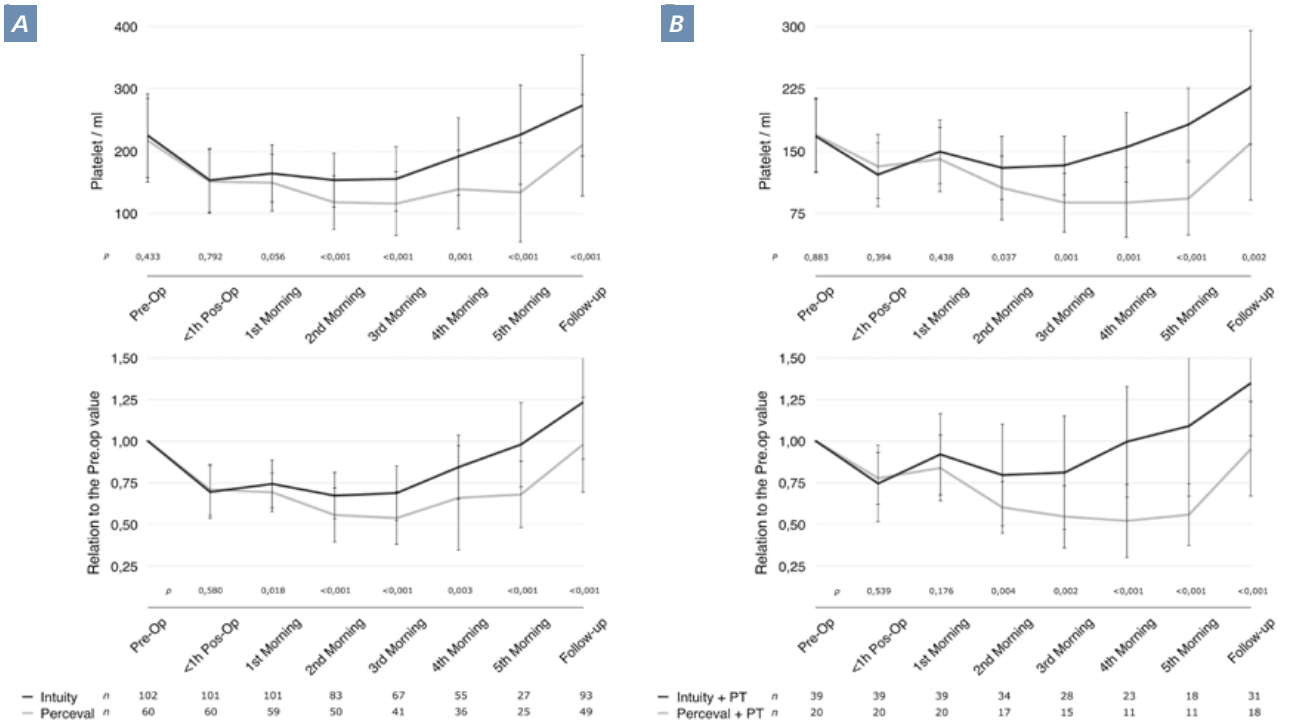

Figure 1

*Comparison of the platelet count in the patients implanted with an Intuity valve and a Perceval valve. The patients that did not received platelet transfusion (**A**) and those who received platelet transfusion (**B**) were analyzed separately.*
PT – Platelet transfusion; <1h Pos-Op – Within 1-hour after surgery; Pre.Op – Preoperative.

vs 64.1%, p<0.001) and a significant increase was found after the transfusion. On the other hand, the low number of patients in the PpG may not be enough to represent the true response.

The results of this study suggest that, compared to those who received an Intuity valve, in the patients that received a Perceval valve: there was one (or more) factor(s) that negatively affect the postoperative platelet count; and the higher drop in platelet count was transient and not enough to increase the risk of bleeding events.

Platelet count and quality can be influenced by multiple preoperative, intraoperative and postoperative factors. Low preoperative count of platelets, intraoperative factors and postoperative renal dysfunction and infection were similar between groups (IG vs PG and IpG vs PpG). Extracorporeal circulation time was overall short in all groups and the differences were small (3.8 minutes higher in the PG [vs IG] and 3.6 minutes higher in the IpG [vs IgP]), therefore this is unlikely the cause. More patients in the IG had coronary disease (vs PG) and were under antiplatelet drugs. For this reason, preoperative antiplatelet drugs cannot explain the drop of platelets in the PG. Heparin-induced thrombocytopenia was not investigated in this study, but it is unlikely that more patients in the Perceval groups were randomly affected. As for postoperative drugs, including antiaggregant drugs, the same therapeutic protocol was applied to all patients. One possible explanation for these results is the valve itself. The Perceval valve was compared to the Intuity valve by Jiritano and colleges[10] and Magna Ease by Mujtaba and colleges.[11] In both cases, the Perceval valve was also associated to a significant, but transient, greater reduction in platelets count, in comparison to Edward's valves. The same was found by Stanger and colleges[12] when they compared Freedom, Perceval S and SOLO valves with non-Sorin valves (mechanical valves, Magna, 3f Enable). As previously mention in the Methods section, the Perceval valve is derived from the stentless Pericarbon Freedom and Freedom SOLO valves and presents the same intense postoperative platelet count drop phenomenon.[13,14] This phenomenon has been on study and debate over the last decade. Platelet activation by anticalcification or storage components (such as homocysteic acid)[12,15], mechanical stress of the prosthesis on the platelet[15] and activation/rupture by the naked nitinol stent[10,11] have been proposed as possible causes. The last two are very unlikely, since the valve has excellent hemodynamic performances and if the stent was the problem, this phenomenon would not occur with the Pericarbon Freedom and Freedom SOLO valves, which are stentless. Strong evidences presented by Stanger and colleges[12,15] suggested that the underlying cause of the severe postoperative platelet count drop associated with Sorin valves was the anticalcification treatment with homocysteic acid. The hypothesis stated that after cardiopulmonary bypass some of the platelets become particularly susceptible to damage and stimulation; once in contact with valve, N-methyl-D-aspartic acid (NMDA)-type glutamate receptors on these "high sensitive" platelets were activated by the homocysteic acid, leading to its lysis. On

the other hand, the platelets not activated by the cardiopulmonary bypass were not affected and remained functionally intact, limiting the potential bleeding complications. In our study, as previously mentioned, platelet transfusion did not result in an increase in platelet count in the patients that receive a Perceval valve. Assuming this result was not a bias of small numbers, based on the previous hypothesis, we could extrapolate that the transfused platelets also became "high sensitive" during the production or delivery process and reacted to the homocysteic acid (or other unknown element). At the moment, we have no further data to support this idea; more studies are needed. Nevertheless, a reassuring fact emerges: the effect of the Perceval valve on platelets does not appear to increase the bleeding risk.

Study limitations

The limitations of this study were linked to the use of data from a single institution, a limited number of cases and data and a different number of patients between groups. Also, it was a retrospective study and only early outcomes were studied.

CONCLUSION

Compared to the Intuity valve, the Perceval valve is associated with a transient, but significant, drop in platelet count. This drop was not associated to an increased risk of bleeding neither in the transfuse group nor the non-transfused group. Platelet transfusion, in this setting, should be judicious and not only ruled by absolute values.

REFERENCES

1. Jacobs JP, Burke RP, Quintessenza JA, Mavroudis C. Congenital Heart Surgery Nomenclature and Database Project: Atrioventricular canal defect. Ann Thorac Surg 2000; 69:S36-S43.
2. Marino B. Congenital heart disease in patients with Down's syndrome: Anatomic and genetic aspects. Biomed Pharmacother 1993; 47:197-200.
3. Karl TR, Provenzano SC, Nunn GR, Anderson RH. The current surgical perspective to repair of atrioventricular septal defect with common atrioventricular junction. Cardiol Young 2010; 20(3):120-7.
4. Rastelli GC, Ongley PA, McGoon DC. Surgical repair of complete atrio-ventricular canal with anterior common leaflet undivided and unattached to ventricular septum. Mayo Clin Proc 1969; 44:335-341.
5. Sabine H, Daebritz, MD. Correction of Complete Atrioventricular Septal Defects With Two Patch Technique. Oper Tech Thorac Cardiovasc Surg 2004; 9:208-220.
6. Geoffrion TR, Singappuli K, Murala JSK. A review of the Nunn modified single patch technique for atrioventricular septal defect repair. Transl Pediatr. 2018; 7(2):91-103.
7. Pan G1, Song L, Zhou X, Zhao J. Complete atrioventricular septal defect: comparison of modified single-patch technique with two-patch technique in infants. J Card Surg 2014; 29(2):251-5.
8. Li D, Fan Q, Iwase T, Hirata Y, An Q. Modified Single-Patch Technique Versus Two-Patch Technique for the Repair of Complete Atrioventricular Septal Defect: A Meta-Analysis. Pediatr Cardiol 2017; 38(7):1456-1464.
9. Xiong Y, Wang L, Liu W, Hankey GJ, Xu B, Wang S. The Prognostic Significance of Right Bundle Branch Block: A Meta-analysis of Prospective Cohort Studies. Clin Cardiol 2015; 38(10):604-13.
10. Harkness WT, Hicks M. Rhythm, Bundle Branch Block, Right (RBBB). StatPearls [Internet] 2018.
11. Harmandar B1, Aydemir NA, Karaci AR, Sasmazel A, Saritas T, Bilal MS, Yekeler I. Results for surgical correction of complete atrioventricular septal defect: associations with age, surgical era, and technique. J Card Surg. 2012 Nov;27(6):745-53.
12. Deraz S, Ismail M. Single patch technique versus double patch technique in repair of complete atrioventricular septal defect. The Egyptian Heart Journal 2013. 66(2): 177-182.
13. Sivalingam S, Krishnasamy S, Al-Fahmi NA et al. Early and midterm outcome of complete atrioventricular septal defect (AVSD) in a single institution. Indian J Thorac Cardiovasc Surg 2013. 29:223–229.
14. Atz AM, Hawkins JA, Lu M et al. Surgical management of complete atrioventricular septal defect: associations with surgical technique, age, and trisomy 21. J Thorac Cardiovasc Surg 2011. 141:1371–1379.
15. Pan G, Song L, Zhou X et al. Complete atrioventricular septal defect: comparison of modified single-patch technique with two-patch technique in infants. J Card Surg 2014. 29:251–255.