

Thrombocytopenia Associated with Perceval Sutureless Aortic Valve Replacement in Elderly Patients: A Word of Caution

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ABSTRACT

Objective: The aim of this study was to report for the first time the phenomenon of thrombocytopenia associated with the use of sutureless aortic valve replacements (AVR), and try to find an explanation for its occurrence.

Methods: The data was collected retrospectively for all patients who had sutureless AVR (7 patients) and was compared to patients who underwent sutured AVR (22 patients) by the same surgeon between February 2012 and November 2013.

Results: Cardiopulmonary bypass and cross-clamp durations were shorter in the sutureless group (96.4 min, 70.6 min) compared to the sutured group (128.3 min, 97.3 min), ($P = .04$, $P = .003$) respectively. Mean transvalvular gradients were lower in the sutureless group (mean = 9.6 mmHg) compared to the sutured group (mean = 17.3 mmHg). Platelet levels were significantly lower in the Perceval patients compared to the Enable patients and sutured valves. Platelet transfusion was higher for sutureless valves (6.5 units versus 5.4 units for the sutured group, $P = .63$), especially the Perceval valve (7.6 units versus 5.3 for the Enable valve, $P = .35$), but was not statistically significant. Packed red blood cells (PRBCs) transfusion was significantly higher in the sutureless group (6 units versus 3.1 for the sutured group, $P = .002$).

Conclusion: The implantation of sutureless aortic valves, especially the Perceval valve, was associated with a significant drop in platelet count postoperatively with slow recovery and higher PRBCs transfusion requirements. Extreme caution should be taken before the routine use of these valves in elderly patients who are already at risk of thrombocytopenia postoperatively.

INTRODUCTION

Open surgical aortic valve replacement (SAVR) has been the standard of care for severe aortic stenosis (AS) for decades. Transcatheter aortic valve replacement (TAVR) was recently approved by the FDA for inoperable and high-risk surgical candidates with isolated AS. However, patients who require combined procedures like mitral

valve replacement (MVR)/ repair or coronary artery bypass grafting (CABG) may not be candidates for TAVR. This group of patients as well as the moderate-risk AS patients may benefit from the use of sutureless valves during isolated SAVR or combined procedures. These sutureless valves have been shown to reduce the cardiopulmonary bypass (CPB) and aortic cross-clamp duration and to facilitate minimally invasive surgery (MIS) [Santarpino 2014; Concistrè 2013; Santarpino 2013; Martens 2010]. The hemodynamic performance of sutureless valves is excellent with low mean and peak transvalvular gradients [Martens 2011; Sadowski 2009; Folliguet 2012; Kocher 2013; Phan 2014], and its use has been associated with excellent short and midterm clinical outcomes [Folliguet 2012; Kocher 2013; Phan 2014].

We noticed from our limited experience with the use of these sutureless valves that they are associated with greater drops in postoperative platelet counts. To our knowledge, this phenomenon was never reported before with sutureless AV and the aim of this study was to report this phenomenon and try to find an explanation for its occurrence.

METHODS

The study was approved by the ethics committee in our hospital and the need for informed consent was waived. The data was collected retrospectively for all patients who had sutureless AVR (7 patients) between February 2012 and November 2013. All the sutureless AVRs were performed by the same surgeon in our institution during that period. Data was collected on all the patients who underwent sutured AVR by the same surgeon during the same time period (22 patients) as a control group. All patients underwent routine CPB with direct aortic and right atrial cannulation. Myocardial protection was achieved using cold blood cardioplegia with 4:1 dilution. A hot shot of 1 L of warm cardioplegia was administered before removal of the aortic cross-clamp. Transesophageal echocardiogram was performed on all patients intraoperatively to measure transvalvular gradients and to assess for any paravalvular leak.

Statistical Analysis

Statistical analysis was performed using NCSS 9 statistical software. Continuous variables were compared using either the two-sample t test or the Wilcoxon rank sum test as appropriate by the distribution of data. Categorical variables were compared using χ^2 test or Fisher's exact test depending on the number of items in each group.

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Patients' Characteristics

	Sutured Valve (n = 22)	Sutureless Valve (n = 7)	P
Sex, female, n (%)	6 (27)	5 (71)	.04
Age, n (%)	55.2 (3.1)*	71.5 (2.6)*	.01
Diabetes mellitus, n (%)	7 (32)	4 (57)	.27
Hypertension, n (%)	12 (55)	7 (100)	.04
Smoking, n (%)	6 (27)	1 (14)	.45
Renal failure, n (%)	–	–	–
Chronic lung disease, n (%)	2 (9)	3 (43)	.04
Ejection fraction, n (%)	57.4 (2.6)*	59.6 (6.3)*	.74
CPB time, minutes	128.3 (6.1)*	96.4 (12.8)*	.04
Cross-clamp time, minutes	97.3 (4.4)*	70.6 (3.8)*	.003

*Mean ± SD

RESULTS

The patients' demographics are reported in the Table. Twelve patients in the sutured AVR group had metallic AV and 10 patients had bioprosthetic AV. In the sutureless group, 3 patients had an Enable valve (Medtronic, ATS Medical, Minneapolis, MN, USA) and 4 patients had a Perceval valve (Sorin Group, Saluggia, Italy). The sutureless AVR group included more females (71%), and older patients (mean = 71.5 years) with more hypertension (100%) and chronic lung disease (43%) compared to the sutured AVR group (27%), (55.2 years), (55%), and (9%) respectively. Upper ministernotomy was utilized in one patient in the sutureless AVR group and 8 patients in the sutured AVR group. Cardiopulmonary bypass and cross-clamp durations were significantly shorter in the sutureless group (96.4 min, 70.6 min) compared to the sutured group (128.3 min, 97.3 min), ($P = .04$, $P = .003$) respectively. There was no intraoperative or perioperative deaths and all patients were extubated 4–6 hours postoperatively. Mean transvalvular gradients were lower in the sutureless group (mean = 9.6 mmHg) compared to the sutured group (mean = 17.3 mmHg). Mild paravalvular leak was detected in two of the patients who had sutureless AVR (both had a Perceval valve) while no paravalvular leaks were detected in any of the sutured AVR group. One patient in the sutureless group tested positive for heparin induced thrombocytopenia (HIT) and his postoperative course was complicated by Ogilvie's syndrome, which was treated conservatively. He was discharged home 2 months postoperatively but was readmitted 1 week later with perforated caecum that required laparotomy and was complicated by infected hematoma that developed in the laparotomy incision. Respiratory complications followed and the patient died with sepsis and multi-organ failure 8 months postoperatively. Another patient in the sutureless group who had a Perceval valve had a prolonged hospital stay of 3 weeks due to lack of mobilization and severe diastolic dysfunction that responded to physiotherapy and diuresis.

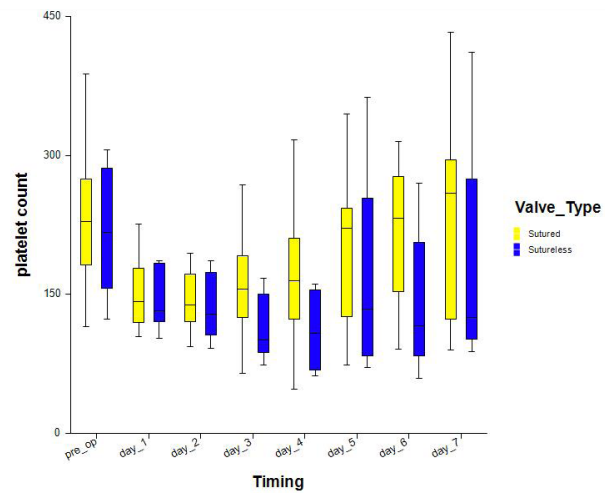


Figure 1. Comparison of postoperative platelet count between sutured and sutureless valves.

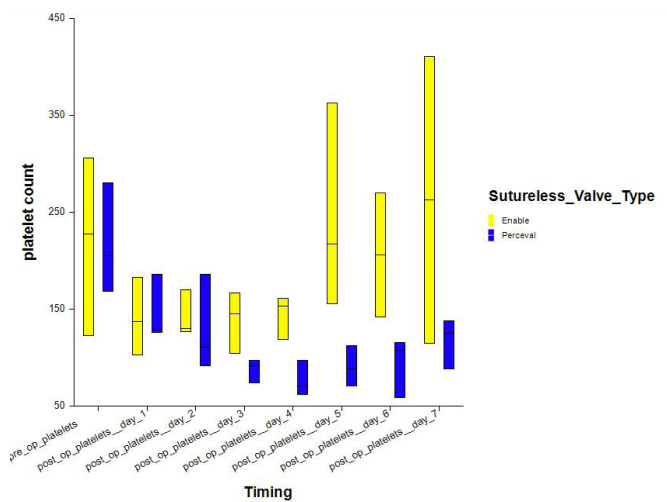


Figure 2. Comparison of postoperative platelet count between Enable and Perceval sutureless valves.

Echocardiogram on discharge showed mild paravalvular leak. She was admitted a month later with congestive heart failure (CHF) and echocardiogram showed moderate to severe paravalvular leak with moderate mitral regurgitation and antero-septal akinesia. The Perceval valve looked distorted in the echo and folded on itself. The patient underwent urgent cardiac catheterization and had a balloon dilatation of the valve that was inflated back to its open position and the paravalvular leak became mild. During the same session, she had a coronary angiogram to investigate the antero-septal akinesia and it showed a complete occlusion of the left anterior descending artery (LAD) that was not amenable to percutaneous intervention. The patient continued to have CHF that responded partially to medical therapy but she died one year later with CHF. All other patients had uneventful postoperative course and were alive and doing well at 1-year follow up.

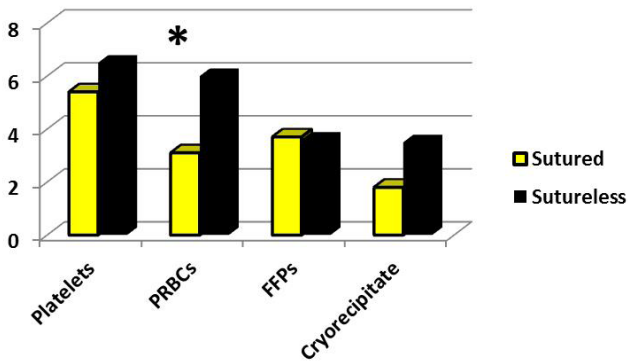


Figure 3. Comparison of postoperative blood products transfusion between sutured and sutureless valves.

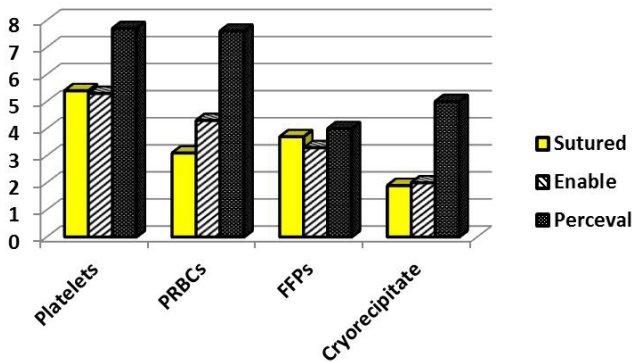


Figure 4. Comparison of postoperative blood products transfusion between sutured and different types of sutureless valves.

Postoperative Thrombocytopenia

All patients experienced a postoperative drop in platelet count as shown in Figure 1. However, the lowest platelet count in the sutured AVR group occurred in the first postoperative day and then started to trend up with full recovery in the 4th to 5th postoperative day. On the other hand, the platelet count continued to drop in the sutureless AVR group until the 4th postoperative day, with slow recovery toward 7 to 10 days postoperatively. The difference in platelet counts between the two groups was not statistically significant at all time points and that is probably related to the low number of patients. When we compared the postoperative platelet count between the two different types of sutureless valves (Figure 2), we found that from the third day on platelet levels were significantly lower in the Perceval patients compared to the Enable patients who followed a similar pattern to the sutured valve patients. Platelet transfusion was higher for sutureless valves (6.5 units versus 5.4 units for the sutured group, $P = .63$) (Figure 3) especially the Perceval valve as in Figure 4 (7.6 units versus 5.3 for the Enable valve, $P = .35$) but was not statistically significant. Packed red blood cells (PRBCs) transfusion was significantly higher in the sutureless group (6 units versus 3.1 for the sutured group, $P = .002$). This difference was attributed to the higher PRBCs transfusion requirement

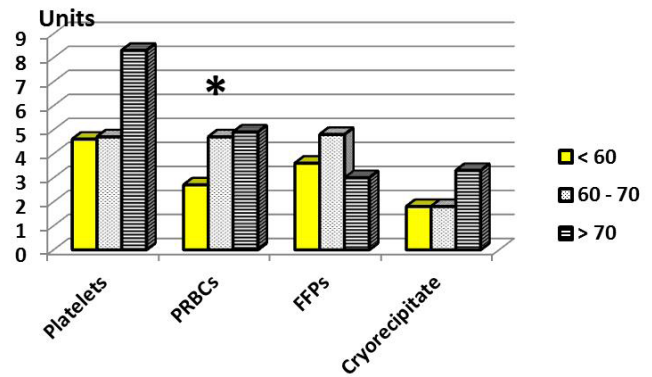


Figure 5. Comparison of postoperative blood products transfusion by age category.

in the Perceval group (7.6 units versus 4.3 for Enable valves, $P = .21$) as shown in Figure 4. There were no differences in other blood products transfusion requirements. Because sutureless valves were more commonly used in elderly patients, we looked at the effect of age on transfusion requirements and we found that patients older than 70 years required more platelet and PRBCs transfusion than younger patients (Figure 5). Finally, two out of four Perceval patients required reexploration for excessive bleeding, while no patients with Enable sutureless or sutured valves required reexploration.

DISCUSSION

We showed in our experience that the use of sutureless valves, especially the Perceval valve, was associated with a significant drop in platelet count with slow recovery associated with higher PRBCs transfusion requirements postoperatively, but not associated with any other significant clinical consequences. To our knowledge, this phenomenon was never reported before in association with the use of sutureless valves.

Thrombocytopenia after SAVR has been reported previously with the stentless Freedom Solo (FS) bioprosthesis (Sorin Group, Saluggia, Italy) by several authors [Yerebakan 2008; Hilker 2009; Piccardo 2010; Repossini 2012; Miceli 2012; van Straten 2010]. This phenomenon occurred in the 2nd and 3rd postoperative days and affected 25-50% of the patients implanted with the FS valves, and platelet drop was as low as 20% of their baseline preoperative level. In the same time, there were multiple reported cases of valve thrombosis necessitating reoperative valve replacement with the FS valves [Hilker 2009; Grubitzsch 2005; Beholz 2007]. However, there were no other complications reported in association with thrombocytopenia related to the use of these FS valves and the phenomenon was transient and resolved without clinical consequences or hemodynamic dysfunction [Yerebakan 2008; Piccardo 2010; Repossini 2012; Grubitzsch 2005]. In our study, the drop in platelet count started to occur during the 3rd postoperative day with slow recovery toward the 7th to 10th days. The lowest drop in platelet count was down to 22% of the preoperative baseline level and occurred in patients implanted with the Perceval valve. The same patient

had evidence of a thrombotic event as confirmed by coronary angiogram showing complete occlusion of the LAD due to embolization. As shown in other studies, there were no other clinical consequences associated with thrombocytopenia that was transient but resulted in more transfusion requirements.

Small valve sizes have been described as causing some turbulence across the valve resulting in platelet activation or destruction, and consequently postoperative thrombocytopenia [Hilker 2009; Piccardo 2010; van Straten 2010]. However, sutureless valves are well known for their superior hemodynamic performance as indicated by the low gradients across these valves, as shown in our study and others. Microhemodynamic effects of the prosthesis structure could trigger the described phenomenon resulting in transient non-specific activation of platelets leading to diffuse consumption and lower platelet levels. The theory of platelet activation was suggested by Le Guyader [Le Guyader 2006], who observed platelet activation after aortic valve replacement with both mechanical and bioprosthetic aortic valves by assessing platelet P-selectin expression, platelet leukocyte conjugate formation, and platelet micro particles. The platelet activation continued for more than 2 months in some patients who were implanted with bioprosthetic valves. Platelet activation could also result from valve manipulation or the presence of the metal stent, similar to the reported thrombocytopenia associated with the TAVI procedures, first reported by Grube et al [Grube 2006]. In the setting of TAVI procedures, several steps of surgical valve replacement that promote platelet activation [Le Guyader 2006; Eslam 2011; Goldsmith 2000; Goldsmith 2001] are present: endothelial damage caused by prosthesis implantation, fibrinogen binding on metallic armatures, and shear stress modifications due to prosthesis implantation [Nobili 2008]. Opposite to the FS valves, thrombocytopenia post-TAVI was reported to be associated with in-hospital major adverse cardiovascular events and was associated with poor outcomes [Gallet 2013]. The sutureless valves combine characteristics of both TAVI and open SAVR. The metal stent in the sutureless AVR may play a role in platelet activation and the possibility of paravalvular leaks, similar to the ones reported with TAVI, and may also trigger platelet activation and consumption. This could especially be because the metal stents of these valves could interfere with the quality of images and could conceal or underestimate the degree of some paravalvular leaks.

Another possible explanation is the transient direct toxic effect of these valves on platelets, caused by the valve preparation material. Similar to the FS valves, the Perceval valve is fixed in a glutaraldehyde and requires minimal rinsing prior to implantation because it is detoxified with homocysteic acid and stored in an aldehyde-free solution. Homocysteine and the product of its spontaneous oxidation, homocysteic acid, have the ability to activate N-methyl-d-aspartate receptors, increasing intracellular levels of ionized calcium and reactive oxygen species. Even a short-term exposure of cells to homocysteic acid can induce an apoptotic transformation [Boldyrev 2009]. Consequently, homocysteic acid can have a damaging effect on vessel endothelial cells, such as inhibition of nitric oxide synthetase, activation of factor V, decrease in activating

action of C-reactive protein, misbalance of thrombomodulin expression, and inhibition of binding of tissue plasminogen activator by endothelial cells. All these effects can precipitate platelet aggregation resulting in both thrombocytopenia and thrombotic complications [Albacker 2010]. However, homocysteic acid is present in healthy humans as a product of the spontaneous oxidization of homocysteine [Boldyrev 2009]. Furthermore, these valves are carefully washed after detoxification with a homocysteic acid-free solution and then stored in jars filled with a homocysteic acid-free storage solution. Consequently, the residual amount of homocysteic acid, which could be transferred to the patient during the valve implantation, is negligible and the resulting concentration in blood is extremely low, so cannot be blamed for the postoperative thrombocytopenia. Pozzoli et al [Pozzoli 2013] investigated the role of rinsing the FS with saline solution before the implantation and found no difference in the postoperative counts in patients who had washing versus those who did not have washing for the implanted valves. This indicates that there should be another explanation for the thrombocytopenia beyond immunologic or toxic effects.

Advanced age and long CPB duration has been suggested by other studies to be associated with postoperative thrombocytopenia [van Straten 2010]. In our study all the sutureless valves were implanted in patients older than 65 years. However, old age was associated with higher platelets and PRBCs transfusion as shown in Figure 5, regardless of the type of valve implanted. Given the small number of patients in this study, it is difficult to separate the effect of age from the effect of the implanted valve on postoperative platelet count. The CPB durations were shorter in the sutureless group than the sutured one so it cannot be responsible for the differential postoperative platelet behavior.

Limitations

This study has several limitations. It was a retrospective study and therefore may have included some bias in data collection. The number of patients in the sutureless group is small. The results could have been affected by unmeasured or hidden covariates. The number of subjects is limited due to the low frequency of the implantation of the sutureless prostheses. Although our comparison groups have multiple differences in their characteristics, we did not include such comparison to provide confirmatory evidence of superiority of one intervention versus the other, but rather to give a snapshot of our regular transfusion practice in the sutured valves, and to shed some light on the settings during which this thrombocytopenia phenomenon was detected. After our report, the experience of other departments with a larger sample of patients should be awaited to strengthen our conclusion.

Conclusion

The implantation of sutureless aortic valves is associated with a significant drop in platelet count postoperatively, with slow recovery and higher PRBCs transfusion requirements. Extreme caution should be taken before the routine use of these valves in elderly patients who are already at risk of thrombocytopenia postoperatively. Further studies with

larger numbers are needed to confirm our findings and to clarify the pathophysiological bases of thrombocytopenia in those patients.

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