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Thrombocytopenia in Moderate- to High-Risk Sutureless Aortic Valve Replacement

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Background: This study aimed to compare preliminary data on the outcomes of sutureless aortic valve replacement (SU-AVR) with those of aortic valve replacement (AVR). **Methods:** We conducted a retrospective study of SU-AVR in moderate- to high-risk patients from 2013 to 2016. Matching was performed at a 1:1 ratio using the Society of Thoracic Surgeons predicted risk of mortality score with sex and age. The primary outcome was 30-day mortality. The secondary outcomes were operative outcomes and complications. **Results:** A total of 277 patients were studied. Ten patients (50% males; median age, 81.5 years) underwent SU-AVR. Postoperative echocardiography showed impressive outcomes in the SU-AVR group. The 30-day mortality was 10% in both groups. In our study, the patients in the SU-AVR group developed postoperative thrombocytopenia. Platelet counts decreased from $225\times10^3/\mu L$ preoperatively to 94.5, 54.5, and $50.1\times10^3/\mu L$ on postoperative days 1, 2, and 3, respectively, showing significant differences compared with the AVR group (p=0.04, p=0.16, and p=0.20, respectively). The median amount of platelet transfusion was higher in the AVR group (12.5 vs. 0 units, p=0.052). **Conclusion:** There was no difference in the 30-day mortality of moderate- to high-risk patients depending on whether they underwent SU-AVR or AVR. Although SU-AVR is associated with favorable cardiopulmonary bypass and cross-clamp times, it may be associated with postoperative thrombocytopenia.

Key words: 1. Sutureless valve replacement
2. Moderate to high risk patient
3. Postoperative thrombocytopenia
4. Aortic valve replacement

Introduction

Aortic stenosis is the most common form of valvular heart disease [1]. The standard treatment for aortic stenosis is surgical aortic valve replacement (AVR) [2]. This operation involves sternotomy with cardiopulmonary bypass (CPB) during the operation. The diseased aortic valve (especially calcific pathology) needs to be resected and replaced with a new valve. However, with the increased age of the at-risk population, older patients with aortic stenosis are at a higher risk during conventional operations because of comorbid disease and a heavily calcified annulus [3]. Up to 30% of aortic stenosis patients are classi-

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fied as high-risk or inoperable [4]. Nonetheless, even optimal medical therapy can result in 1-year mortality as high as 30%–50% [1]. Currently, transcatheter aortic valve replacement (TAVR) is gaining acceptance as the treatment of choice in intermediate- to high-risk patients [5]. The results of TAVR in patients with aortic stenosis had higher rate of vascular complications. In addition, conclusion on valve durability can not be drawn due to limitations regarding length of follow-up. The rate of 30-day major adverse events after TAVR ranges from 3% to 35% [6]. One reason for the high incidence of complications in TAVR is that the replacement of a tissue valve over a diseased calcified native valve can cause unpredictable damage to the calcified structure. Moreover, in patients who decide to undergo combined cardiac surgery (e.g., myocardial revascularization, other valve repair/replacement, or the maze procedure), TAVR is not a suitable solution.

Momentum within the field returned to the previous concept of AVR. Therefore, AVR needs to be performed more rapidly and safely in order to avoid compromised hemodynamic and clinical outcomes in intermediate- to high-risk patients, who are considered to be in a gray zone regarding this procedure. There have been many studies of the rapid deployment of sutureless aortic valve replacement (SU-AVR), especially after the Food and Drug Administration approved this method in 2009. This technique has the benefit of rapid deployment without leaving any knots in the aortic valve annulus. SU-AVR also involves resecting and decalcifying the diseased valve, which is known to be best for patients.

Despite the benefits of SU-AVR, which include better hemodynamics in patients with a small aortic annulus [7], shorter CPB and cross-clamp times [7-12], and facilitating minimally invasive valve surgery [7,13], strong indications for SU-AVR remain unclear. Prospective clinical studies of high-risk patients showed that the 30-day and 1-year mortality rates were not inferior to conventional AVR [8,14], and no significant differences were found in terms of complications [15].

Methods

Symptomatic patients with severe aortic stenosis who underwent SU-AVR were matched with patients who underwent AVR during the study period. The indications for AVR and SU-AVR followed the American College of Cardiology/American Heart Association 2014 [2] and/or the European Society of Cardiology 2012 [16] guidelines on the management of valvular heart disease. After matching, demographic data were collected, including patients' characteristics, underlying disease, and details of surgery. Preoperative, intraoperative, and postoperative (days 3–7) echocardiograms were obtained. The primary outcome was 30-day mortality. The secondary outcomes were perioperative and intraoperative outcomes and complications, including echocardiographic data. Echocardiographic findings, complications, and clinical outcomes were compared between the groups.

1) Definitions

AVR was defined as conventional AVR with a stented aortic tissue valve replacement. SU-AVR was defined as sutureless AVR. TAVR was defined as transfemoral or transapical TAVR. Low-risk patients had a Society of Thoracic Surgeons (STS) score of <4. Intermediate-risk patients had an STS score of ≥ 4–8. High-risk patients had an STS score of ≥ 8.

2) Data collection

This was a retrospective cohort study that was performed from January 2013 to May 2016. We carried out 1:1 matching of the SU-AVR and AVR groups, using the STS predicted risk of mortality (PROM) score with sex and age. All patients with symptomatic aortic stenosis were included. The exclusion criteria were as follows: (1) inoperable patients who were assessed by the heart team; (2) patients who underwent TAVR; (3) low-risk patients (STS score <4); (4) patients with a bicuspid aortic valve; (5) patients with a mechanical aortic valve; (6) patients with dissection or dilatation of the ascending aorta; (7) patients with a sinotubular junction/annulus ratio >1.3 (as a contraindication for the Perceval valve); (8) patients with known hypersensitivity to nickel alloys; (9) patients with an aortic annulus <19 millimeter or >27 millimeter, which was not compatible with the Perceval valve; (10) patients with previous or concomitant root aneurysm; and (11) patients with a recent history of stroke.

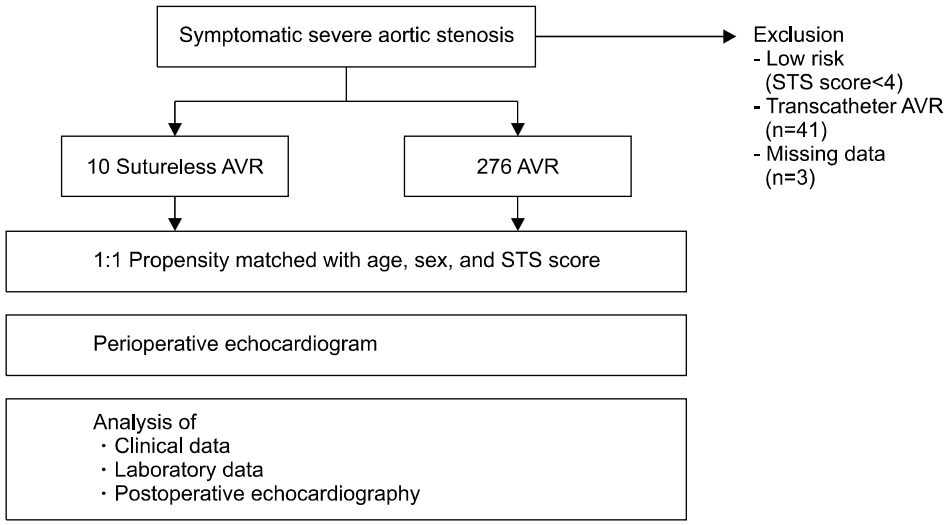

Fig. 1. Schema of 1:1 propensity matching. STS, Society of Thoracic Surgeons; AVR, aortic valve replacement.

3) Operative procedure

All AVR operations included in this study were performed via the full median sternotomy approach. CPB was established with the cardioplegic arrest technique. An aortic incision was made in either an oblique or transverse fashion above the sinotubular junction. The diseased aortic valve was meticulously excised. The aortic annulus was decalcified by rongeur forceps or a no. 11 knife for proper valve positioning. The new valve was prepared after measurement of the aortic annular diameter. Either a sutured or sutureless valve was replaced. Double-layered aortotomy was performed for closing the incision.

(1) Conventional aortic valve replacement: All AVR procedures were performed with a bovine pericardial tissue valve replacement. The suture technique depended on the surgeon's preference for either multiple simple stitches or a mattress suture with pledgets. Supra-annular valve positioning was achieved in all AVR procedures.

(2) Sutureless valves: All SU-AVRs were performed with a Perceval S prosthesis (Sorin/LivaNova Group, Saluggia, Italy) and this sutureless valve was made of bovine pericardium. The valve was prepared to shrink before insertion and expansion. Three threads were sutured at the nadir of each sinus of Valsalva to the button hole at the Perceval valve. These threads were used as a reference line for alignment and to avoid malrotation. The valve was parachuted through the aortotomy incision to the aortic annulus. After the valve was released from mounting, augmented expansion with pneumatic balloon dilatation pressure at 4 atm for 40 seconds was performed at the level of the annulus. The 3 hanging sutures were removed later.

4) Statistical analysis

After matching was performed, demographics, comorbidities, and outcomes of interest were compared using the chi-square test or the Fisher exact test and the t-test for categorical and continuous variables, respectively. Results are expressed as mean±standard deviation or median with interquartile range (IQR). Repeated continuous variables were compared using 1-way analysis of variance. All analyses were performed using IBM SPSS for Windows ver. 22.0 (IBM Corp., Armonk, NY, USA). All p-values <0.05 were considered to indicate statistical significance.

Results

The results of 318 patients who were diagnosed with symptomatic severe aortic stenosis were initially analyzed. After the exclusion criteria were applied, there were 267 patients in the AVR group and 10 in the SU-AVR group (Fig. 1). STS PROM matching analysis was performed at a 1:1 ratio (Table 1).

Demographic data, including sex, age, STS score, underlying disease, urgency of surgery, and type of surgery, are shown in Table 2. A total of 10 (5 men; median age, 81.5 years) patients underwent SU-AVR,

Table 1. Matching of SU-AVR and AVR patients

Patient	SU-AVR (n=10)			AVR (n=10)			p-value
	Sex	Age (yr)	STS score	Sex	Age (yr)	STS score	
1	M	67	4.12	M	67	4.537	0.143
2	M	72	4.61	F	72	4.842	
3	F	73	4.24	F	73	4.176	
4	F	78	4.3	F	82	4.048	
5	M	78	5.08	M	77	4.778	
6	F	88	8.24	M	88	8.568	
7	F	92	33.264	F	91	9.635	
8	M	85	48.71	M	83	11.98	
9	F	93	49.41	F	90	14.979	
10	M	89	78.99	F	88	34.844	

SU-AVR, sutureless aortic valve replacement; AVR, aortic valve replacement; STS, Society of Thoracic Surgeons; M, male; F, female.

Table 2. Demographic data

Variable	Sutureless AVR (n=10)	AVR (n=10)	p-value
Sex (male)	5 (50)	4 (40)	0.655
Age (yr)	81.5±9.1	81.1±8.4	0.758
Society of Thoracic Surgeons score	6.66 (4.28–48.88)	6.70 (4.44–12.72)	0.143
Diabetes mellitus	5 (50)	6 (60)	0.705
Hypertension	10 (100)	8 (80)	0.168
Renal failure	0 (0)	1 (10)	NA
History of smoking	3 (30)	1 (10)	0.317
Coronary artery disease	7 (70)	6 (60)	0.608
New York Heart Association class ≥3	5 (50)	5 (50)	1.0
Echo: ejection fraction	55.10±17.57	57.06±17.64	0.84
Aortic valve area (cm^2)	0.67±0.34	0.51±0.33	0.313
Timing, emergency	5 (50)	2 (20)	0.25
Redo surgery	2 (20)	0 (0)	NA
Combined valve surgery	2 (20)	2 (20)	1
Combined coronary artery bypass graft	5 (50)	6 (60)	0.705

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
AVR, aortic valve replacement; NA, not applicable.

and were matched at a 1:1 ratio using the STS PROM score to 10 patients who underwent AVR in the study period. Sutureless valves were successfully implanted in 9 of the 10 patients. The valve size was small in 1, medium in 5, and large in 4 patients in the SU-AVR group. The valve size was 21 mm in 4 patients, 23 mm in 5 patients, and 25 mm in 1 patient in the AVR group. The median STS score was 6.66 (IQR, 4.28–48.88) in the SU-AVR group and 6.70 (IQR, 4.44–12.72) in the AVR group. The most common presenting symptom was progressive dyspnea with a mean functional class of 3. The median CPB time was 120 minutes (IQR, 102–176.7 minutes) in the SU-AVR group and 148 minutes (IQR, 113–175.5 minutes) in the AVR group (p=0.607) (Fig. 2). The median cross-clamp duration was 93.5 minutes (IQR, 67–129 minutes) in the SU-AVR group and 124 minutes (IQR, 98.5–149.5 minutes) in the AVR group (p=0.140) (Fig. 2). The 30-day mortality was the same in the SU-AVR and AVR groups (10%). One-year mortality was also the same in the SU-AVR and AVR groups (10%). Two patients in the SU-AVR group required a redo operation because of paravalvular leakage. At 24 months of follow-up, the rates of freedom from valve-related mortality, stroke, acute myocardial infarction, endocarditis, and pros-

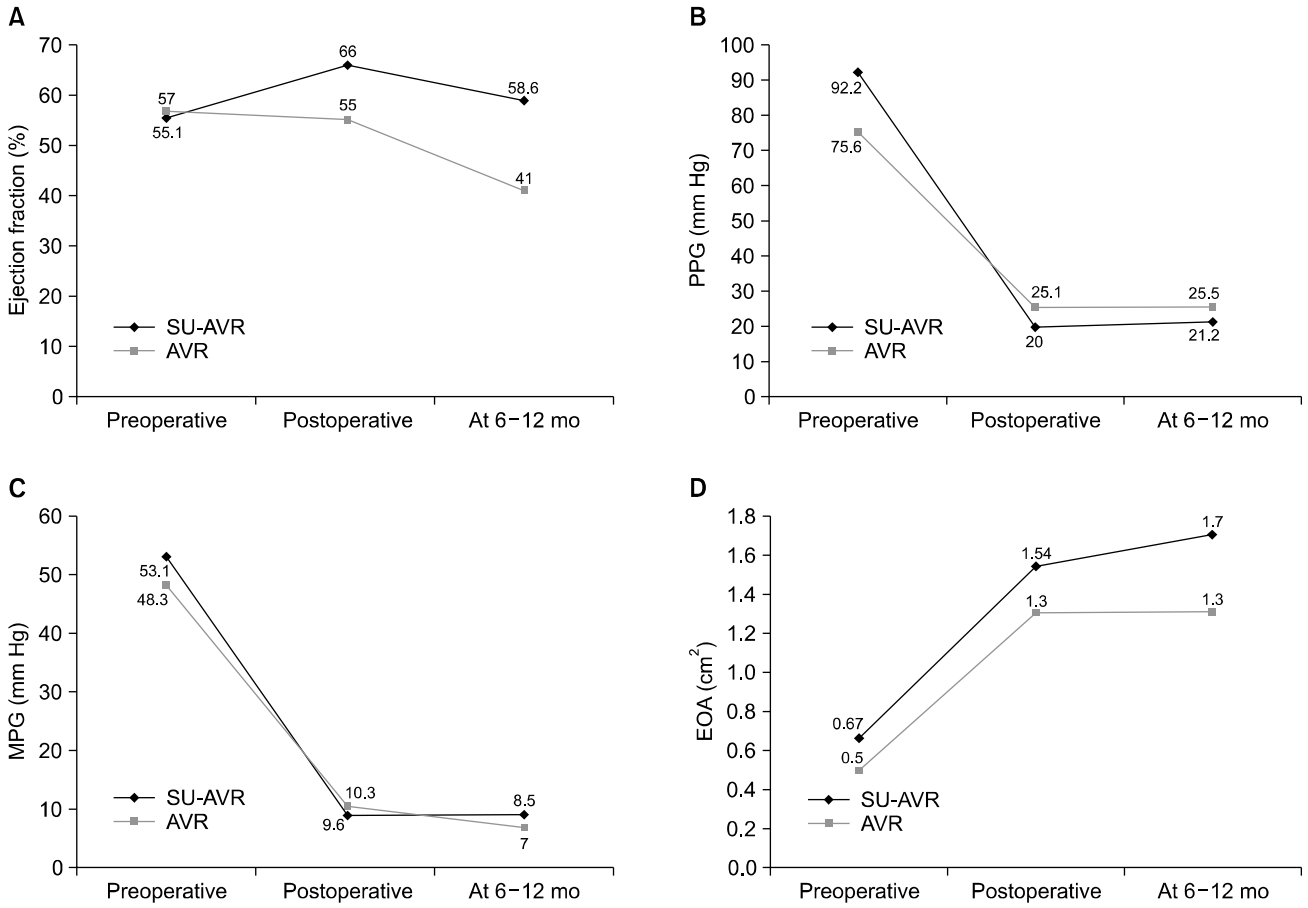

Fig. 2. (A) Ejection fraction, (B) PPG (mm Hg), (C) MPG (mm Hg), and (D) EOA (cm2). SU-AVR, sutureless aortic valve replacement; AVR, aortic valve replacement. PPG, peak pressure gradient; MPG, mean pressure gradient; EOR, effective orifice area.

thesis regurgitation were 100%, 100%, 100%, 100%, and 90%, respectively, in the SU-AVR group. One patient in the SU-AVR group developed moderate regurgitation during follow-up.

At postoperative follow-up, patients in the SU-AVR and AVR groups had a median functional class of I. Postoperative echocardiography showed impressive outcomes in the SU-AVR group, with a reduced mean pressure gradient from 53.1 to 9.6 mm Hg postoperatively and 8.5 mm Hg at follow-up without left ventricular impairment (ejection fraction: 55.1% preoperatively, 66% postoperatively, and 58.6% at 6–12 months of follow-up; p=0.41) (Fig. 3). The effective orifice area of the aortic valve increased from 0.67 to 1.54 cm^2 in the SU-AVR group and from 0.51 to 1.3 cm^2 in the AVR group (Fig. 3).

The median blood transfusion (packed red cells) was 2 units (IQR, 1–3.25 units) in the SU-AVR group

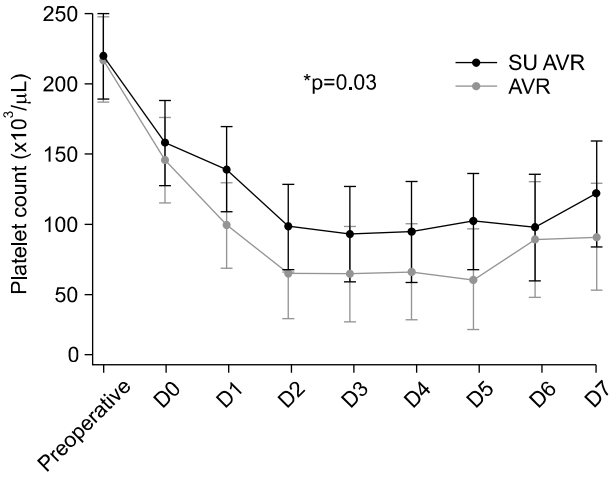

Fig. 3. Comparison of platelet counts between the SU-AVR and AVR groups. SU-AVR, sutureless aortic valve replacement; AVR, aortic valve replacement; D, postoperative day. *p＜0.05.

Table 3. Procedural and clinical outcomes

Variable	Sutureless AVR (n=10)	AVR (n=10)	p-value
Cardiopulmonary bypass time (min)	120 (102–176.75)	148 (113–175.5)	0.607
Cross-clamp time (min)	93.5 (67–129)	124 (98.5–149.5)	0.140
Para/perivalvular leakage	1 (10)	0	0.343
30-day mortality	1 (10)	1 (10)	1.00
In-hospital mortality	1 (10)	1 (10)	1.00
Neurological complication	0	1 (10)	NA
Surgical bleeding with reoperation	3 (30)	0	0.211
Pneumonia	1 (10)	1 (10)	1.00
Acute renal failure	2 (20)	1 (10)	1.00
Liver failure	0	0	NA
Tracheostomy	1 (10)	1 (10)	1.00
Atrial fibrillation	1 (10)	3 (30)	0.582
Pacemaker implantation	0	0	NA
Bleeding dysfunction[a)]	10 (100)	1 (10)	<0.001
Length of hospital stay (day)	15.5 (11–23.5)	20.5 (14–27.75)	0.057
Intensive care unit stay (day)	3.82±1.75	3.59±1.81	0.89

Values are presented as median (interquartile range), number (%), or mean±standard deviation.
AVR, aortic valve replacement; NA, not applicable.
[a)]Defined as bleeding which led to therapeutic treatment, transfusion or led to death.

and 1.5 units (IQR, 1–3.25 units) in the AVR group (p=0.870). The amount of fresh frozen plasma provided was not significantly different between the SU-AVR and AVR groups (1.5 units [IQR, 0–3 units] versus 1 unit [IQR, 0–2.5 units], p=0.758). However, in our study, the patients in the SU-AVR group developed postoperative thrombocytopenia. The preoperative platelet counts were similar between the SU-AVR and AVR groups ($225\times10^3/\mu L$ versus $194\times10^3/\mu L$, p=0.76). However, the platelet counts decreased to 94.5, 54.5, and $50.1\times10^3/\mu L$ on postoperative days 1, 2, and 3 in the SU-AVR group, compared with 135.5, 93.4, and $91.8\times10^3/\mu L$ in the AVR group, respectively (p=0.03, p=0.16, and p=0.20, respectively). Bleeding dysfunction was clinically and statistically significant in the SU-AVR group (p< 0.001) (Table 3). Platelet transfusion was triggered at a platelet count $<30\times10^3/\mu L$ or if patients had signs of bleeding. Therefore, platelet transfusion amounts tended to be higher in the SU-AVR group than in the AVR group (leukocyte-poor platelet concentrations: 12.5 units [IQR, 1.0–20.0 units] versus 0 unit [IQR, 0–10 units], p=0.052) (Fig. 4). In 3 patients in the SU-AVR group, the platelet count was less than $30\times10^3/\mu L$. Two of these patients had to undergo a repeated sternotomy to stop the bleeding, and the other was only given platelet transfusions.

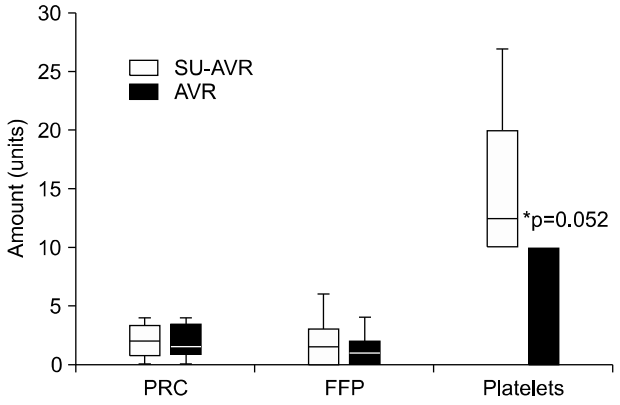

Fig. 4. Amount of blood and blood components transfused. SU-AVR, sutureless aortic valve replacement; AVR, aortic valve replacement; PRC, packed red cells; FFP, fresh frozen plasma. *p< 0.05.

One patient who underwent a re-sternotomy had prolonged thrombocytopenia for nearly 2 weeks, which required a higher amount of platelet transfusion. This patient eventually experienced septic shock, leading to death.

Discussion

A recent systematic review and meta-analysis showed that SU-AVR is a safe procedure associated

with a shorter cross-clamp time and CPB duration than the conventional approach, as well as comparable complication rates [15]. Our study further confirmed these findings, especially in moderate- to high-risk patients. SU-AVR was associated with a reduction in the mean cross-clamp time of 30.5 minutes (25.6% relative reduction) and the CPB time was also reduced by 28 minutes (18.9% relative reduction). The differences in the cross-clamp and CPB times were not significantly different between the groups, but in high-risk patients, these times may have more of an effect than in low-risk patients.

A previous propensity analysis also showed that SU-AVR was associated with a shorter length of stay in the hospital (10.9±2.7 days versus 12.4±4.4 days, $p < 0.001$) and a shorter intensive care unit stay (2.0±1.2 days versus 2.8±1.3 days, $p < 0.001$) compared with conventional AVR [12,17]. However, the population in our study, with a relatively higher risk of comorbid disease, did not show a significantly shorter intensive care unit stay. We believe that the length of stay in the intensive care unit and the hospital would decrease with a higher volume and experience of cases.

In our study, we observed severe postoperative thrombocytopenia after tissue valve replacement, which is uncommon. We observed that all patients who underwent SU-AVR with the Perceval valve had a decrease in their platelet count, from an average of $225\times10^3/\mu L$ preoperatively to $50.1\times10^3/\mu L$ on postoperative day 3. Patients who underwent SU-AVR were also significantly more likely to experience bleeding dysfunction and required a greater amount of platelet transfusion. A previous study showed that the Pericarbon Freedom, Perceval, and SOLO bioprotheses (all from the Sorin Group) were associated with a significantly greater decrease in the postoperative platelet count compared with non-Sorin valves (13% reduction; 95% confidence interval, 11%–145%) [17]. That previous study also showed that anti-calcification treatment or storage solutions from the Sorin Group may have caused acute and chronic toxic effects. In our study, age, sex, and combined surgery were not associated with a decreased platelet count. Furthermore, we did not find a significant association between a smaller valve size and postoperative thrombocytopenia, which was previously described in a previous study [18]. The term "postoperative thrombocytopenia" was defined using a cut-off platelet count of $< 50\times10^3/\mu L$. This definition was described as relatively subjective in some studies, but most studies used a cut-off value of $30–50\times10^3/\mu L$ [18-20]. In our study, we used $30\times10^3/\mu L$ as a trigger for platelet transfusion. As mentioned above, thrombocytopenia after CPB can also found with other types of valves. It is mainly caused by hemodilution, platelet dysfunction, and mechanical valve replacement. Therefore, we minimized these confounding factors by excluding cases of mechanical valve replacement and by using STS PROM matching analysis.

SU-AVR was performed with the Perceval valve, which is a new-generation bovine pericardium sutureless valve design for supra-annular positioning using only 3 hanging sutures to navigate the proper orientation and position. This design was surgeon-friendly and showed excellent early hemodynamic results in our study.

1) Conclusion

SU-AVR may be a new paradigm of AVR in terms of a shorter CPB time, shorter aortic cross-clamp time, and ease of use. However, our small STS PROM matching analysis showed the disadvantage of postoperative thrombocytopenia, requiring transfusion of more blood and blood components. We failed to find any significant differences in the clinical outcomes between the AVR and SU-AVR groups. There were no differences in 30-day mortality or in-hospital mortality between the 2 groups, and no significant differences were found for other complications, except for postoperative thrombocytopenia. The echocardiographic results appeared impressive in the SU-AVR group, but these results were not significantly different from those in the AVR group.

2) Limitations

This study has some limitations. First, this study was only a retrospective STS PROM-matched analysis cohort study. Therefore, we might not have reached the level of analysis that would be found in a randomized controlled trial. Second, although this study was conducted with a relatively high volume of cases, experiences of SU-AVR in Thailand remain limited compared with experiences elsewhere in the world. Third, this study investigated intraoperative

and short-term results. Therefore, a longer follow-up time is required in future studies.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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