Simple Interrupted Suturing for Aortic Valve Replacement in Patients with Severe Aortic Stenosis

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Background: Attaining an adequate effective orifice area (EOA) is definitive goal in aortic valve replacement (AVR). The simple interrupted suture (SIS) technique could be a solution to achieve this goal, but limited data are available in the literature. This study aimed to compare hemodynamic differences between the SIS and non-everting mattress suture (NMS) techniques.

Methods: From our database, 215 patients who underwent AVR for severe aortic stenosis were extracted to form the overall cohort. From March 2015 to November 2016, the SIS technique was used in 79 patients, while the NMS technique was used in 136 patients. Hemodynamic outcomes were evaluated, as detected by transthoracic echocardiography and computed tomography.

Results: There were no significant differences in baseline characteristics between the 2 groups. On immediate postoperative echocardiography, the SIS group showed a significantly wider EOA (1.6±0.4 vs. 1.4±0.5 cm², p=0.007) and a lower mean pressure gradient (PG) (13.3±5.4 vs. 17.0±6.0 mm Hg, p<0.001) than the NMS group. On follow-up echocardiography, the SIS group continued to have a wider EOA (1.6±0.4 vs. 1.4±0.3 cm², p<0.001) and a lower mean PG (11.0±5.1 vs. 14.1±5.5 mm Hg, p<0.001). There was no significant difference in paravalvular leakage.

Conclusion: The SIS technique for AVR was associated with a wider EOA and a lower mean PG. The SIS technique could be a reasonable option for AVR.

Keywords: Aortic valve surgery, Heart valve prosthesis, Surgery techniques, Effective orifice area, Patient prosthetic mismatch

Introduction

Aortic valve replacement (AVR) is the treatment of choice for symptomatic severe aortic stenosis (AS) [1]. As the detrimental effects of patient-prosthesis mismatch (PPM) on long-term survival and regression of the hypertrophied left ventricle (LV) are well acknowledged, implanting a large prosthesis to obtain an adequate effective orifice area (EOA) has remained an essential part of AVR [2,3]. Therefore, in recent decades, manufacturers have attempted to improve the prosthesis design to increase the EOA and to relieve blood flow obstruction, thereby providing better hemodynamics [4].

In addition, the suture technique may also affect hemodynamics after AVR [5]. The traditional standard suture technique used for AVR is the pledgeted non-everting mattress suture (NMS). Although the use of pledgets may be effective in preventing paravalvular leakage (PVL) [6], it may hamper the implantation of a larger prosthesis by reducing the annular diameter. In contrast, recent studies have suggested that AVR using the simple interrupted suture (SIS) technique may provide a larger EOA, thereby allowing the implantation of larger prostheses [7,8]. Additionally, pannus formation, which is the most common cause of redo aortic valve surgery in mechanical valves, may be related to the suture technique [7,9]. However, the relationship between suture techniques and hemodynamic performance has not yet been elucidated [9]. Thus, we
compared the hemodynamic outcomes of the conventional NMS and SIS techniques after AVR to test the hypothesis that the SIS technique could be a more reasonable option to achieve a better EOA after AVR.

Methods

Study population

This study was approved by the Institutional Review Board of Asan Medical Center (approval no., 2020-0558), and the requirement for informed consent from individual patients was waived due to the retrospective nature of the study. We reviewed the institutional cardiac surgery database and identified 581 patients with severe AS who underwent AVR with a supra-annular prosthesis between March 2015 and November 2016. After the exclusion of patients who underwent concomitant mitral and tricuspid valve replacement, redo aortic valve surgery, and AVR using other suture techniques, the remaining 215 patients formed the study population. Patients who underwent concomitant valve replacement were excluded because this procedure makes it difficult to measure the hemodynamic performance of the aortic valve on echocardiography.

The SIS technique was used in 79 patients (SIS group), and NMS technique was used in 136 patients (NMS group). At our institution, for the SIS technique, 15 to 25 (median suture number, 20.5) 2-0 polyester sutures were used in a simple interrupted manner. For the NMS technique, using 2 needles, 11 to 23 (median suture number, 14) 2-0, Ethibond pledged sutures were passed from the LV side through the aortic side of the annulus to the sewing ring of the prosthetic valve. The prosthetic valve size was determined by its original valve size. Regardless of the suturing method, the prosthetic valve was securely seated on the annulus and sutures were passed through its sewing cuff.

Outcomes of interest and data collection

The primary outcomes of interest were the measured EOA and mean pressure gradient (PG) on echocardiographic evaluation in the SIS and NMS groups. The other outcome of interest was the incidence of PVL after AVR in the 2 groups. Patient characteristics, medical risk factors, and operative profiles were retrospectively evaluated. Hemodynamic and anatomical profiles detected by echocardiography and computed tomography (CT) were also evaluated. Hemodynamic profiles including left ventricular ejection fraction (LVEF), EOA, EOA index (ratio of the EOA to the body surface area), peak and mean PG, left ventricular outflow tract (LVOT) diameter, and PVL were collected retrospectively from echocardiographic assessments at 3 different time points: preoperative, immediately postoperative (within 5 days after AVR), and follow-up postoperative (median follow-up duration, 9.6 months after AVR; interquartile range, 5.8–12.9 months).

The annulus size was calculated by obtaining the average of the long axis and short axis of the annulus diameter, which was measured on CT images. The EOA was evaluated using Doppler echocardiography and the continuity equation using the velocity-time integral [10]. PVL was defined as an abnormal paravalvular regurgitant jet outside the prosthetic valve ring on follow-up echocardiography.

Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Data are expressed as mean and standard deviation for continuous variables and as frequencies and percentage for categorical variables. We compared patients’ characteristics, surgical profiles, and hypothermia (30°C–35°C). The native aortic valve leaflet was excised, crushed, and calcium fragments were removed carefully from the diseased annulus.

At our institution, for the SIS technique, 15 to 25 (median suture number, 20.5) 2-0 polyester sutures were used in a simple interrupted manner. For the NMS technique, using 2 needles, 11 to 23 (median suture number, 14) 2-0, Ethibond pledged sutures were passed from the LV side through the aortic side of the annulus to the sewing ring of the prosthetic valve. The prosthetic valve size was determined by its original valve size. Regardless of the suturing method, the prosthetic valve was securely seated on the annulus and sutures were passed through its sewing cuff.
preoperative and postoperative hemodynamic profiles between the 2 groups using the chi-square test or the Fisher exact test for categorical variables and the Student t-test for continuous variables. For all comparisons, p-values of 0.05 or less were considered to indicate statistical significance.

**Results**

The demographics of the patients, clinical risks, and echocardiographic profiles of both groups are shown in Table 1. The patients in the NMS group were older than those in the SIS group. The prevalence of comorbidities was similar between the 2 groups. In the echocardiographic profiles, the rate of bicuspid aortic valve did not differ significantly between the 2 groups (57.0% versus 47.1%, p=0.203). LVEF tended to be higher in the SIS group than in the NMS group. The aortic valve area (0.63±0.17 versus 0.64±0.15 cm$^2$, p=0.686) and LVOT diameter (20.9±1.6 versus 21.1±1.7 mm, p=0.373) were similar between the 2 groups. The AV annulus diameter measured on CT scans was also similar between the 2 groups. The operative data are shown in Table 2. Out of the 141 patients who underwent isolated AVR, 79.0% (n=58) were in the SIS group and 60.4% (n=83) were in the NMS group. The profiles of concomitant surgical procedures were not significantly different between the 2 groups. The proportion of mechanical and bioprosthetic valves was also similar in both groups. The most commonly used mechanical valves in the SIS and NMS groups were SJM Regent valves (St. Jude Medical, St. Paul, MN, USA) and ATS AP valves (Medtronic, Minneapolis, MN, USA), respectively. The most commonly used bioprosthesis was Perimount Magna valves (Edwards Life Sciences, Irvine, CA, USA) in both groups. Although there was no statistically significant difference in the anulus diameter between the 2 groups before surgery, larger prosthetic valves were more commonly used in the SIS group, and the prosthesis-to-annulus size ratio tended to be higher in the SIS group than in the NMS group (0.94±0.09 versus 0.89±0.07, p<0.001). Minimally invasive cardiac surgery was more commonly employed in the SIS group than in the NMS group (58.2% versus 17.6, p<0.001). Moreover, there was no significant difference in

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**Table 1. Baseline characteristics and hemodynamic profiles in the SIS group and NMS group (N=215)**

| Characteristic                      | SIS group (n=79) | NMS group (n=136) | p-value |
|-------------------------------------|------------------|-------------------|---------|
| **Baseline characteristics**        |                  |                   |         |
| Age (yr)                            | 65.1±9.7         | 68.0±7.9          | 0.016   |
| Male sex                            | 46 (58.2)        | 88 (64.7)         | 0.382   |
| Body surface area (m$^2$)           | 1.7±0.2          | 1.7±0.1           | 0.056   |
| Body mass index (kg/m$^2$)          | 24.6±4.0         | 24.8±3.2          | 0.698   |
| Hypertension                        | 45 (57.0)        | 73 (53.7)         | 0.672   |
| Diabetes mellitus                   | 16 (20.3)        | 28 (20.6)         | >0.99   |
| Hyperlipidemia                      | 28 (35.4)        | 52 (38.2)         | 0.770   |
| Chronic kidney disease              | 5 (6.3)          | 6 (4.4)           | 0.537   |
| Dialysis                            | 4 (5.1)          | 5 (3.7)           | 0.728   |
| Chronic obstructive pulmonary disease| 4 (5.1)        | 14 (10.3)         | 0.211   |
| Atrial fibrillation                 | 5 (6.3)          | 13 (9.6)          | 0.457   |
| Peripheral artery occlusive disease | 18 (22.8)        | 32 (23.5)         | >0.99   |
| Cerebrovascular accident            | 8 (10.1)         | 11 (8.1)          | 0.625   |
| Hemoglobin                          | 12.9±1.9         | 12.9±1.6          | 0.736   |
| **Echocardiography measurements**  |                  |                   |         |
| LVEF (%)                            | 60.5±9.7         | 57.6±12.8         | 0.085   |
| LVEF <40%                           | 5 (6.3)          | 21 (15.4)         | 0.053   |
| Aortic valve area (cm$^2$)          | 0.63±0.17        | 0.64±0.15         | 0.686   |
| Peak PG (mm Hg)                     | 105.2±28.4       | 101.3±32.0        | 0.370   |
| Mean PG (mm Hg)                     | 63.9±18.1        | 61.4±20.4         | 0.361   |
| Bicuspid aortic valve               | 45 (57.0)        | 64 (47.1)         | 0.203   |
| Left ventricular outflow tract diameter (mm) | 20.9±1.6 | 21.1±1.7 | 0.373   |
| **Computed tomography measurement**|                  |                   |         |
| AV annulus diametera (mm)           | 24.7±3.0         | 25.1±3.1          | 0.255   |

Values are presented as mean±standard deviation or number (%), unless otherwise indicated. SIS, simple interrupted suture; NMS, non-everting mattress suture; LVEF, left ventricular ejection fraction; PG, pressure gradient; AV, aortic valve.

aThe AV annulus diameter was the mean value of the long and short axes.
CPB time (118.6±38.2 versus 113.5±41.0 minutes, p=0.36) or aortic cross-clamp time (76.9±27.4 versus 78.1±28.2 minutes, p=0.77).

The immediate postoperative and follow-up echocardiographic profiles are shown in Table 3. On immediate postoperative echocardiography, the SIS group showed a significantly wider EOA (1.6±0.4 versus 1.4±0.5 cm², p=0.007) and lower mean transaortic PG (13.3±5.4 versus 17.0±6.0 mm Hg, p<0.001) than the NMS group. Furthermore, on follow-up echocardiography, the SIS group had a wider EOA (1.6±0.4 versus 1.4±0.3 cm², p<0.001) and lower mean transaortic PG (11.0±5.1 versus 14.1±5.5 mm Hg, p<0.001) than the NMS group.

The incidence of significant PVL (≥grade 3) did not differ significantly between the 2 groups. All patients who developed PVL after surgery were asymptomatic and they were treated medically and kept under close observation at our outpatient clinic.

A subgroup analysis was performed to evaluate the relationship between aortic annulus size and the impact of different suture techniques (Table 4). Patients with a relatively small aortic annulus (prosthetic valve size, 18–23 mm) treated with the SIS technique showed a significantly wider EOA (1.49±0.4 versus 1.32±0.3 cm², p<0.01) and lower mean transaortic PG (16.8±6.4 versus 21.1±7.5 mm Hg, p<0.01) than those treated with the NMS technique. However, patients with a relatively large aortic annulus (prosthetic valve size >23 mm) did not show a significantly different EOA between the SIS and NMS groups (1.74±0.4 versus 1.6±0.3 cm², p=0.06).

Table 2. Surgical profiles of the SIS group and NMS group (N=215)

| Variable | SIS group (n=79) | NMS group (n=136) | p-value |
|----------|-----------------|------------------|---------|
| Prosthesis type | | | |
| Mechanical valve | 33 (41.8) | 41 (30.1) | 0.102 |
| ATS AP | 6 (18.2) | 24 (58.5) | |
| Bicarbon | 3 (9.1) | - | |
| On-X | 4 (12.1) | 2 (4.9) | |
| Overline | 3 (9.1) | - | |
| SJM Regent | 17 (51.5) | 15 (36.6) | |
| Bioprosthesis | 46 (58.2) | 95 (69.9) | 0.102 |
| Perimount Magna | 26 (56.5) | 39 (41.1) | |
| Hancock bioprosthesis | 4 (8.7) | 38 (40.0) | |
| Mitroflow | 2 (4.3) | 9 (9.5) | |
| Mosaic bioprosthesis | - | 2 (2.1) | |
| Trifecta | 14 (30.4) | 7 (7.4) | |
| Valve size (mm) | | | |
| 18–20 (prosthesis) | 7 (8.9) | 21 (15.4) | |
| 21–22 (prosthesis) | 20 (25.3) | 51 (37.5) | |
| 23–24 (prosthesis) | 29 (36.7) | 39 (28.7) | |
| 25–27 (prosthesis) | 23 (29.1) | 25 (18.4) | |
| Prosthesis-annulus size ratio | 0.94±0.09 | 0.89±0.07 | <0.001 |
| Minimally invasive approach | 46 (58.2) | 24 (17.6) | <0.001 |
| Isolated aortic valve repair | 58 (73.4) | 83 (61.0) | 0.075 |
| Concomitant procedure | 21 (26.6) | 53 (39.0) | 0.075 |
| Aortic surgery | 8 (10.2) | 21 (15.4) | |
| Bypass surgery | 5 (6.3) | 23 (16.9) | |
| Valve repair surgery | 5 (6.4) | 6 (4.4) | |
| Arhythmia surgery | 6 (7.7) | 7 (5.3) | |
| Atrial septal defect repair | 2 (2.5) | 2 (1.5) | |
| Cardiopulmonary bypass time (min) | 118.6±38.2 | 113.5±41.0 | 0.36 |
| Aortic cross clamp time (min) | 76.9±27.4 | 78.1±28.2 | 0.77 |

Values are presented as number (%) or mean±standard deviation, unless otherwise indicated. Valve names are sorted in ascending alphabetical order: ATS AP (Medtronic Inc., Minneapolis, MN, USA), Bicarbon (Sorin Group USA Inc., Arvada, CO, USA), Hancock bioprosthesis (Medtronic Inc., Minneapolis, MN, USA), Mitroflow (Sorin Group USA Inc., Arvada, CO, USA), Mosaic bioprosthesis (Medtronic Inc., Minneapolis, MN, USA), On-X (On-X Life Technologies Inc., Austin, TX, USA), Overline (Sorin Group USA Inc., Arvada, CO, USA), Perimount Magna (Edwards Lifesciences, Irvine, CA, USA), SJM Regent (St. Jude Medical Inc., St. Paul, MN, USA), and Trifecta (St. Jude Medical Inc., St. Paul, MN, USA).

SIS, simple interrupted suture; NMS, non-everting mattress suture.
Table 3. Postoperative valve performance data from echocardiography (N=215)

| Variable | SIS group (n=79) | NMS group (n=136) | p-value |
|----------|------------------|-------------------|---------|
| **First postoperative echocardiography (within 5 days)** | | | |
| LVEF (%) | 60.3±8.4 | 58.3±10.9 | 0.184 |
| EOA (cm²) | 1.6±0.4 | 1.4±0.5 | 0.007 |
| EOA index (cm²/m²) | 1.0±0.2 | 0.9±0.3 | 0.021 |
| Peak PG (mm Hg) | 24.6±9.9 | 31.1±11.1 | <0.001 |
| Mean PG (mm Hg) | 13.3±5.4 | 17.0±6.0 | <0.001 |
| LVOT diameter (mm) | 20.4±1.5 | 20.1±1.7 | 0.285 |
| PVL | 1 (1.3) | 7 (5.1) | 0.451 |
| Trivial | 0 | 3 | |
| Mild | 1 | 3 | |
| Mild to moderate | | | |
| Second follow-up echocardiography | | | |
| LVEF (%) | 63.2±5.6 | 61.8±7.1 | 0.150 |
| EOA (cm²) | 1.6±0.4 | 1.4±0.3 | <0.001 |
| EOA index (cm²/m²) | 0.9±0.2 | 0.8±0.2 | 0.001 |
| Peak PG (mm Hg) | 20.5±8.4 | 26.1±9.6 | <0.001 |
| Mean PG (mm Hg) | 10.9±5.1 | 14.1±5.4 | <0.001 |
| LVOT diameter (mm) | 20.1±1.4 | 20.2±1.5 | 0.766 |
| PVL | 3 (4.2) | 9 (6.6) | 0.39 |
| Trivial | 1 | 3 | |
| Mild | 2 | 4 | |
| Mild to moderate | | | |
| Third follow-up echocardiography | | | |
| PVL | 5 (6.4) | 14 (10.3) | 0.3 |
| Trivial | 2 | 2 | |
| Mild | 2 | 9 | |
| Mild to moderate | 1 | 3 | |

Values are presented as mean±standard deviation or number (%), unless otherwise indicated.
SIS, simple interrupted suture; NMS, non-everting mattress suture; LVEF, left ventricular ejection fraction; EOA, effective orifice area; PG, pressure gradient; LVOT, left ventricular outflow tract; PVL, paravalvular leakage.

Table 4. Subgroup analysis of postoperative valve performance on the second follow-up echocardiography according to prosthetic valve size (N=215)

| Variable | SIS group | NMS group | p-value |
|----------|-----------|-----------|---------|
| **Valve size 18–23 mm** | | | |
| No. of patients | 52 | 108 | |
| EOA (cm²) | 1.49±0.4 | 1.32±0.3 | <0.01 |
| EOA index (cm²/m²) | 0.92±0.2 | 0.81±0.2 | <0.01 |
| Peak PG (mm Hg) | 21.9±8.7 | 27.4±10.0 | <0.01 |
| Mean PG (mm Hg) | 16.8±6.4 | 21.1±7.5 | <0.01 |
| **Valve size >23 mm** | | | |
| No. of patients | 27 | 28 | |
| EOA (cm²) | 1.74±0.4 | 1.6±0.3 | 0.06 |
| EOA index (cm²/m²) | 1.0±0.3 | 0.9±0.2 | 0.15 |
| Peak PG (mm Hg) | 17.3±7.0 | 22.4±7.0 | 0.02 |
| Mean PG (mm Hg) | 13.2±5.1 | 17.1±5.2 | 0.03 |

Values are presented as mean±standard deviation or number, unless otherwise indicated.
SIS, simple interrupted suture; NMS, non-everting mattress suture; EOA, effective orifice area; PG, pressure gradient.

*Median follow-up duration (1–3 quartile): 9.6 months (interquartile range, 5.8–12.9 months)."
Discussion

In this study, more patients in the SIS group than in the NMS group had favorable hemodynamic values, with a wider EOA and lower transaortic PG, after AVR. It was also possible to implant larger prosthetic valves using the SIS technique, and there was no significant difference in the incidence of PVL between the 2 groups.

Obtaining a greater EOA and lower transaortic PG are surgical goals in AVR. The relationship between the suture technique and hemodynamic efficiency after AVR has been investigated in some recent studies. Tabata et al. [7] and Kim et al. [9] reported that pledgeted mattress sutures were disadvantageous in terms of hemodynamic performance, as that technique reduced the EOA in small aortic roots. In contrast, Ugur et al. [6] found no difference according to the suture method and stated that there was no relationship between the EOA and suture technique. Based on the results of previous studies, there have been ongoing discussions about which suture technique is more advantageous to obtain better hemodynamics. In this study, we found that SIS had hemodynamic benefits than NMS during AVR.

First, compared to the NMS technique, we obtained a larger prosthesis-to-annulus size ratio with the SIS technique. There is lack of evidence to support the claim that only the suture technique would make it possible for a surgeon to implant a larger prosthetic valve. However, the suture technique might have a positive impact on valve size. When undergoing AVR surgery, the implantation of a large prosthesis is known to be effective in obtaining a large EOA, and a large EOA is associated with a low risk of PPM. This is known to be a predictor of potentially poor long-term clinical prognosis. When determining the size of the prosthetic valve, not only is the diameter of the patient’s native annulus important, but the suture technique should also be considered. In this study, the baseline mean aortic valve annulus diameter measured on CT images were statistically similar in both groups, but the SIS group had larger valve implants than the NMS group. It is possible that when performing the NMS technique, pledgets could decrease the annulus diameter to less than 1 mm, whereas this does not happen when the SIS technique is used [5,7].

No scientific research has explored the interference of pledgets on the annulus diameter; however, when we determined the maximal diameter of the annulus with a valve-sizer to implant larger prostheses, the maximal diameter tended to be smaller after pledget suturing than before.

Second, the SIS technique might produce a wider EOA, a low PG, and a lower risk of PPM after AVR, irrespective of the size of the prosthetic valve. A possible theory for explaining the wider EOA in the SIS group is that subvalvular rolling might take place during the NMS technique. In the NMS technique, pledgets pull the annular tissue up medially into the valve frame; therefore, the LVOT is reduced. However, the native LVOT is preserved in the SIS technique because in this technique, tissue rolling does not occur [7,11].

One of the major complications after the replacement of a prosthetic valve is PVL, which is usually related to disruption of the annular tissue during the sewing ring suture. PVL after AVR is rare, but it may lead to serious complications. The pledgets in the NMS technique can protect the tissue from being cut through during tying and have been proposed to decrease the incidence of PVL after AVR [12]. Therefore, there might be a concern that if the SIS technique is done without pledgets, the incidence of PVL could increase. However, in our study, there was no significant difference in the incidence of PVL between the SIS and NMS groups. None of the PVL events in this study led to hemodynamically significant consequences or hemolysis.

Among the types of prosthetic valve dysfunction after AVR, abnormal tissue ingrowth such as pannus formation arising from the LV side is the most common cause of redo surgery in patients who undergo AVR with a mechanical prosthesis. Another advantage of the SIS technique is that the risk of tissue ingrowth after AVR caused by foreign substances such as pledgets may be relatively small compared to the corresponding risk in the NMS technique [7,9]. In this respect, long-term follow-up studies should investigate the incidence of redo AVR surgery caused by pannus formation according to whether the SIS or NMS technique is used.

In patients with a small aortic annulus who undergo AVR, a small prosthesis is implanted, and patients with a small aortic annulus are more likely to experience PPM. However, patients with a large aortic annulus have a relatively minimal risk of PPM compared to those with small aortic roots [9]. The choice of the suture technique—with or without pledgets—could be an important factor for achieving a better EOA. Our subgroup analysis showed significant differences in EOA and PG between the SIS and NMS groups only in patients who received relatively small prostheses. In this regard, the hemodynamic differences between the SIS and NMS techniques would be more pronounced in patients with a small aortic root, in whom the SIS technique might be a better option for AVR.

Limitations

There are a few limitations of our study. First, the present...
study had the limitation of being a nonrandomized, retrospective analysis conducted at a single institution over a relatively short period of time. Therefore, further studies investigating the long-term clinical outcomes of hemodynamics or complications between the 2 different suture techniques may be needed. Conducting a further analysis among only patients who receive bioprostheses or those who receive mechanical prostheses would more clearly show the effects of the suture technique itself. Second, we only analyzed hemodynamic outcomes measured using echocardiography. Therefore, further studies analyzing other factors that could influence clinical outcomes would be needed.

In addition, surgeon-related factors could influence the hemodynamic results. At our institution, there are 5 expert cardiac surgeons who have sufficient and long-term clinical experience (more than 10 years). Therefore, their aortic valve surgical results would not be expected to be different.

Conclusion

The choice of using the SIS technique or NMS technique for AVR was investigated in relation to obtaining a larger EOA and low mean PG, which may reduce the incidence of PPM without increasing the risk of PVL. The SIS technique could be a reasonable option for AVR.

Conflict of interest

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

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