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The Use of Vascular Closure Devices and Impact on Major Bleeding and Net Adverse Clinical Events (NACE) in Balloon Aortic Valvuloplasty: A Sub-Analysis of the BRAVO study

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Abstract

Objective—To determine the impact of suture-mediated vascular closure devices on net adverse clinical events (NACE) after balloon aortic valvuloplasty (BAV).

Background—Ischemic and bleeding complications are common following transfemoral BAV however; previous studies have been single center and limited by varying definitions of major bleeding.

Methods—The Effect of Bivalirudin on Aortic Valve Intervention Outcomes (BRAVO) study was a retrospective observational study conducted at two high-volume academic centers over a 6-year period designed to compare the effect of bivalirudin versus unfractionated heparin. This is a sub-analysis of 428 consecutive patients who underwent BAV (with 10-13 French sheaths) to compare the effect of hemostasis with vascular closure devices versus manual compression utilizing standardized definitions. NACE was defined as the composite of major bleeding and major adverse clinical events (MACE). All events were adjudicated by an independent clinical events committee who were blinded to antithrombin use.

Results—Pre-closure was performed in 269 (62.8%) of patients. While bivalirudin was used more frequently in those with pre-closure (60.6% vs. 37.7%, $p<0.001$), a history of prior BAV (11.1% vs. 3.6%, $p=0.04$) and peripheral vascular disease (30.7% vs. 19.7%, $p=0.01$) was more common in those not undergoing pre-closure ($n=159$, 37%). Other clinical and demographic features were well balanced between groups. Vascular closure was associated with a significant reduction in NACE (24.5% vs 10.0% $p<0.001$). Results remained significant after adjusting for baseline differences and bivalirudin use (OR 0.38, 95% CI: 0.21 - 0.68; $p=0.001$).

Conclusions—Our study suggests that suture-mediated vascular closure is associated with a substantial reduction in NACE after transfemoral BAV. Large randomized clinical trials should be conducted to confirm our results.

Keywords

Balloon Aortic Valvuloplasty; Aortic Stenosis; Bleeding; Closure devices

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Introduction

Transcatheter aortic valve replacement (TAVR) has given hope to patients with aortic stenosis (AS) who were previously deemed inoperable. With the proliferation of this technology, there has been a resurgence in the use of balloon aortic valvuloplasty (BAV) as a bridge to TAVR. Despite advances in technology such as the use of non-compliant balloons and rapid ventricular pacing, the safety of the procedure is constrained by several factors. First, the size of the valvuloplasty balloons require placement of large bore arterial access sheaths (up to 13 French). This large sheath size can lead to vascular complications, and bleeding requiring blood transfusions. Second is the nature of the patient population. AS is a disease of the elderly, a subgroup with an elevated risk of bleeding.(1) In addition to bleeding, these patients are also at risk for other complications including stroke and renal insufficiency. (2)

The effects of blood transfusion and bleeding on BAV outcomes are not well characterized. Much of our knowledge is derived from the literature on acute coronary syndromes and surgery. (3) (4) This evidence suggests that bleeding or blood transfusions lead to increased length of Intensive care unit and overall hospital stay, as well as increased rates of recurrent ischemia and death.(3-5) Despite this overwhelming evidence highlighting the deleterious effects of bleeding, as well as our improved ability to identify high-risk patients, an analysis from the National Cardiovascular Data Registry (NCDR) of over 1.5 million patients undergoing percutaneous coronary intervention (PCI) showed an underutilization of strategies to decrease bleeding in those patients whom were at the highest risk. (6) Given the larger size of arterial sheaths in BAV, similar strategies are needed to improve the safety of the procedure. Vascular closure devices (VCDs) have been shown to be a safe alternative to manual compression to achieve hemostasis after cardiac catheterization with 6-8 French sheaths and after structural heart disease interventions with large bore sheaths. (7) (4,8,9) Most previous studies have been single center and limited by varying definitions of major bleeding. It is because of this variation, in addition to lack of adequately sized randomized controlled trials that professional associations have not endorsed their routine use to limit vascular access complications.(10,11) There is a paucity of outcome data available in the literature in regards to major adverse events and bleeding with use of VCDs in elderly patients with AS undergoing BAV. We conducted a two-center observational analysis of patients undergoing BAV followed by hemostasis by either manual compression or VCDs utilizing standardized definitions.

Methods

Patients and Hemostasis Technique

The Effect of Bivalirudin on Aortic Valve Intervention Outcomes (BRAVO) study was a retrospective observational study conducted at two academic medical centers designed to compare the effect of bivalirudin versus unfractionated heparin and the effect of hemostasis with vascular closure versus manual compression in BAV. The registry was a retrospective observational analysis of 428 patients undergoing BAV between BAV 1/1/2005 and 12/31/2010 at Mount Sinai Medical Center, and 11/6/2010 to 7/28/2011 at the University of Miami Hospital, 159 with manual compression and 269 with vascular closure devices. When hemostasis was achieved using manual compression, the femoral sheath was removed when the activated clotting time (ACT) was less than 180 seconds. Vascular closure was performed using the "Pre-Closure" technique utilizing 2 Proglide devices (Perclose, Abbott Vascular, Redwood City, California). The choice of hemostasis method was at the discretion of the operator performing the procedure.

Definitions and Outcome Measures

The primary outcome measures of our analysis were major bleeding as defined by grade three or greater bleeding according to the Bleeding Academic Research Consortium (BARC) (12) and net adverse clinical events (NACE) defined as the composite of all-cause mortality, myocardial infarction (MI), stroke, and major bleeding. Secondary outcome measures included minor and major bleeding according to Thrombolysis In Myocardial Infarction (TIMI), (13) Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO), (14) and Valve Academic Research Consortium (VARC) definitions, (15) vascular injury according to VARC, major adverse cardiovascular events defined as a composite of all-cause mortality, myocardial infarction, and stroke. Patients were “frail” if they were either bedbound, dependent for all activities of daily living, had moderate or severe dementia, or were a nursing home resident. All hospital endpoints were independently adjudicated by independent clinical events committee (CEC) utilizing source documentation when available and blinded to the hemostatic method utilized. This study was approved by the institutional review boards of the participating institutions.

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean, standard deviation (SD), median (25th, 75th percentile) as appropriate. Categorical variables were compared using chi square or Fisher exact tests and Continuous variables were compared using the two-tailed Student *t*-test for or Wilcoxon Rank Sum test as considered appropriate. To determine independent predictors of major bleeding and NACE, we performed multivariable analyses using logistic regression. Selection of candidate variables was performed by backward stepwise selection. The significance levels for removal and addition of covariates from the model were 0.1 and 0.2, respectively. Candidate variables considered were the use of preclosure (vs. manual compression), age, gender, warfarin, frailty, anemia, use of bivalirudin (vs. heparin), peripheral arterial disease (defined by the presence of claudication or previous or planned intervention on the abdominal aorta or limb arteries), eGFR, concomitant bleeding, prior BAV, the number of arterial access sites used and logistic Euroscore. A 2-tailed *p* value <0.05 was considered statistically significant. All statistical analysis was performed using Stata version 11.2 statistical software (StataCorp, College Station, Texas).

Results

Baseline characteristics were similar in both comparison groups, as depicted in Table 1. The majority of the patients were elderly females. The median Euroscore was high and a substantial proportion of patients were frail. There was a lower incidence of peripheral vascular disease in the preclosure group as compared to the manual compression group, as well as a higher use of bivalirudin with preclosure (Table 2). The use of contrast dye was significantly higher (222±50.4ml versus 136±60.1ml) in the preclosure group *p* <0.0001.

The effect of closure devices on the rates of major bleeding using the various definitions is shown in figure 1. There was a significant reduction in the rates of BARC 3 from 14.5% to 5.6% (*p*=0.01) with manual pressure versus preclosure, respectively. Similar results were observed using other criteria for major bleeding. In addition, we found a lower rate of vascular injury with the use of preclosure (4.8% vs. 10.1% *p*=0.04) (Figure 2). Rates of death and MI were similar between the two groups.

Figure 3 shows the effect of preclosure on MACE and NACE. There was a significant reduction in MACE (13.2% vs. 6.3% *p*=0.02) and NACE (24.5% vs 10.0% *p*<0.001) with

the use of preclosure. Multivariable analysis demonstrated that use of preclosure was independently associated with a significant reduction in the occurrence of NACE. (Table 3)

Discussion

The results of our study suggest the use of the preclosure technique with two suture-mediated VCDs may help decrease bleeding and NACE in patients undergoing BAV. We also found a trend toward decreased rates of death and MI in association with preclosure.

Preclosure has been shown to be effective in previous studies of percutaneous closure of large arterial sheaths. Lee et al performed 262 endovascular repairs using the Preclose technique with two Perclose devices placed prior to the introduction of 12 to 24F sheaths. They demonstrated a 94.3% success rate, shorter overall procedure time, and a vascular complication rate of 5.7% with preclosure.(16) A more definitive analysis of the effectiveness of preclosure will emerge from the the Percutaneous Endovascular Aneurysm Repair (PEVAR) Trial (NCT01070069). This randomized trial comparing the preclose method with standard repair after endovascular abdominal aortic aneurysm repair completed enrollment in October of 2011. Our results expand the favorable evidence for successful use of the Preclose technique to high-risk elderly patients undergoing BAV with large arterial access sheaths.

The ability to achieve reliable and early hemostasis is an important advantage of closure devices particularly in the era of structural heart disease. Many times, patients undergo prolonged procedures under moderate sedation. After completion of the procedure, they must wait for their anticoagulation to reach subtherapeutic levels. When the sheath is removed, they are subject to manual compression for upwards of 45 minutes depending on the size of the sheath, with the patient having to lay supine for 6-8 hours after removal. In patients with severe lower back pain, this can prove especially difficult and may lead to early mobilization which can cause bleeding. Vascular closure devices have been shown to decrease the time to ambulation after cardiac catheterization and therefore offer an attractive option. (7)

Because of the lack of standard definitions, it has been difficult to compare bleeding rates across previous BAV registries. In the NHLBI registry, a 20% rate of blood transfusion of at least 1 unit of blood was reported post-procedurally(17). A more contemporary BAV registry in high-risk or inoperable patients reported blood transfusion rates of 17.6%.(18) Our study is the first BAV registry using BARC definitions. These definitions were recently validated in a pooled analysis of 6 randomized trials in patients undergoing PCI. In this study, a bleeding BARC 2 was associated with a significant increase in 1-year mortality which was comparable to TIMI (major and minor) and REPLACE-2 (major) definitions.(19) BARC definitions will likely become the standard in future clinical trials, allowing for reliable comparison of bleeding rates. In addition to comparing BARC rates of major bleeding with closure devices vs. manual compression, we reported bleeding according to other commonly used definitions such as TIMI, GUSTO, and VARC, especially created for transcatheter valve interventions. We found statistically significant decreases in bleeding for each definition used. Our results compare favorably to a recent single center study of closure devices in BAV with a blood transfusion rate of 21.6% with the use of the Proglide system (18).

Previous studies have failed to show a consistent relationship between MACE and the use of closure devices. In a study including 5,091 patients undergoing PCI comparing manual compression versus the Angioseal device, there were no differences in MACE (2.1% vs. 2.3% p=0.797).(20) This trial excluded patients who underwent procedures with greater than

10-French sheaths. A more recent study which used a primary endpoint of NCDR major bleeding comparing closure devices with manual compression in the setting of PCI showed a similar rate of myocardial infarction (6.5% vs. 5.9% $p=0.55$).⁽²¹⁾

The use of preclosure was favorable with respect to NACE in our study. The experience of combined safety and efficacy endpoints is robust in the literature with respect to PCI (22) (23,24). Previous studies of closure devices in BAV have primarily looked at rates of bleeding or vascular complications alone.^{9,11,15} The interpretation of combined safety and efficacy endpoints can at times be difficult, especially when individual components of the composite endpoint are diverging (25). In our study however, both bleeding and MACE were significantly decreased with the use of preclosure, suggesting a real clinical benefit for this technique. In addition, multivariable analysis showed that use of VCDs was independently associated with a decreased NACE.

We found in our study a significantly higher amount of contrast use (86 cc's) with pre-close versus the no-preclose group. This was unlikely due to the use of the preclose device as at most 2-3 additional angiographic views of the arterial access site were performed in the preclose group to ensure adequate position of the arterial stick in the common femoral artery prior to deployment and to ensure there was no extravasation of contrast or dissection after deployment of the preclose devices. Rather, this is more likely explained by the type of intervention which may have been performed with the valvuloplasty, such as complex native coronary artery intervention or intervention to vein grafts.

Historically, overall vascular complications in valvuloplasty have ranged from 5-11% (17,26). Contemporary studies continue to show a rate within these margins (18). Vascular complications can be associated with significant morbidity, additional surgical procedures, as well as increased length of hospital stay. Additional studies in valvuloplasty showed a similar complication rate of 6.7% with Perclose, and a much higher rate with manual compression of 17.1%. (27). Our results compare favorably with these studies.

Limitations

Our study had a retrospective design without random allocation of treatments, therefore the results are subjected to selection bias. The majority (78.7%) of procedures were performed by one center. Therefore, variations in local practices between the two centers may have affected the overall results of the study. In both centers however, the number of valvuloplasties and use of preclosure was similar amongst the individual operators who were all very experienced in structural heart disease interventions. We did not record the factors which may or may not have influenced the individual operators for their use of closure devices versus manual compression. The decision to use a closure device in BRAVO was left to the operator's discretion. Although Perclose has previously been shown to be safely deployed in smaller case series' in calcified vessels (28), the lower proportion of peripheral vascular disease in the preclosure group highlights the careful selection of patients in whom preclosure was to have the greatest chance of success. The level of the activated clotting time (ACT) was not systematically recorded with the deployment of the preclosure sutures which may have affected the rate of bleeding.

Conclusion

Our experience indicates that use of VCDs in BAV is associated with a net clinical benefit over manual compression for arterial hemostasis. Randomized clinical trials of closure devices versus manual compression in BAV are therefore warranted.

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ABBREVIATIONS LIST

TAVR	Transcatheter aortic valve replacement
AS	Aortic Stenosis
BAV	Balloon Aortic Valvuloplasty
PCI	Percutaneous coronary intervention
VCD	Vascular closure devices
BARC	Bleeding Academic Research Consortium
NACE	Net adverse clinical events
MACE	Major adverse clinical events

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Figure 1.

Comparisons of alternate bleeding definitions according to pre-closure use. VARC bleeding was composite of life threatening and major, TIMI was composite of major and minor, GUSTO was composite of severe or life threatening and moderate, BARC 3 was any transfusion with overt bleeding, overt bleeding plus Hb drop ≥ 5 g/dL or intracranial hemorrhage.

Figure 2. Effect of Pre-Closure on Death, MI, and acute vascular injury. Myocardial infarction was according to VARC definition. Acute vascular injury included perforation, arteriovenous fistula, dissection, pseudoaneurysm, perforation or rupture.

Figure 3.
Effect of Pre Closure of MACE and NACE

Table 1

Baseline Characteristics

	No-Preclosure n=159	Preclosure n=269	p-value
Age	83.6±8.86	83.8±8.94	0.68
Male	42.1%	47.2%	0.31
Hypertension	91.2%	91.4%	0.93
Diabetes	30.8%	36.8%	0.21
Smoking History	50%	46.5%	0.48
Previous MI	27.7%	26%	0.71
Previous CVA	18.9%	14.9%	0.28
Previous CABG	26.4%	23.4%	0.49
Previous PCI	26.8%	19.7%	0.09
Concomitant CAD	40.9%	43.5%	0.60
1 or more previous BAVs	10.7%	3.9%	<0.01
Peripheral Arterial Disease	30.8%	20.1%	0.01
Chronic Kidney Disease	89.1%	83.4%	0.11
Dialysis	6.5%	3.6%	0.21
COPD	23.9%	21.9%	0.64
Afib/flutter	39%	41.6%	0.59
Anemia	67.9%	66.5%	0.77
CHF NYHA III/IV	82.9%	81.4%	0.70
Moderate-Severe LV dysfunction	27.3%	33.3%	0.41
Exertional Syncope	11.3%	10%	0.68
Frailty	16.4%	18.6%	0.56
EUROSCORE (median)	31.9%	30.4%	0.92

Table 2

Procedural Characteristics

	No-Preclosure n=159	Preclosure n=269	p-value
Hospital LOS (median days)	3.0	3.0	0.10
Total Contrast volume (ml)	136±60.1	222±50.4	<0.0001
Arterial access sites used			
1 Artery	62.3%	71%	0.06
2 Arteries	37.7%	29%	0.06
Vascular Cut Down	0%	0.4%	0.44
Access site bleeding	13.8%	4.6%	0.01
Pre-closure attempted	...	269	...
Pre-closure successful	...	98.1%	...
Largest BAV balloon used (diameter in mm)	22.0±1.43	21.6±2.16	0.03
Rapid RV Pacing	45.9%	30.1%	<0.01
Use of Bivalirudin	37.7%	60.6%	<0.01

Table 3

Independent Predictors of NACE

	OR (95% CI)	P value
Pre-closure	0.38 [0.21, 0.68]	<0.01
Bivalirudin (vs. heparin)	0.56 [0.31, 1.01]	0.05
EUROSCORE	4.54 [1.09, 18.9]	0.04
Frailty	2.00 [1.03, 3.88]	0.04
Anemia	1.86 [0.97, 3.57]	0.06
Female gender (vs. male)	1.67 [0.92, 3.02]	0.09