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Exposure to glucocorticoids prior to transcatheter aortic valve replacement is associated with reduced incidence of high-degree AV block and pacemaker

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ABSTRACT

Background: Tissue edema and inflammation, which occur at the device landing zone during valve deployment, may contribute to the pathophysiology of conduction abnormalities after transcatheter aortic valve replacement (TAVR). We hypothesized that exposure to glucocorticoids prior to TAVR will reduce the incidence of conduction abnormalities requiring PPM implantation after TAVR.

Methods: We included 167 consecutive patients treated with TAVR at the Minneapolis VA Medical Center and University of Minnesota. Exposure to glucocorticoids was assessed by linking electronic medical and pharmacy records. The primary outcome was a new PPM within 30 days of the index TAVR procedure.

Results: Of the 167 patients included, 16 (9.5%) were exposed to glucocorticoids prior to TAVR. No differences in age, STS score, pre-existing right bundle branch block, implantation depth or valve type were seen among patients exposed to glucocorticoids versus those who were unexposed. Patients exposed to glucocorticoids were more likely to have moderate/severe COPD (43% versus 18%, $p < 0.01$). The cumulative incidence of PPM implantation at 30-days after TAVR was 18%. None of the patients exposed to glucocorticoids required a PPM while 30 (19%) of the unexposed patients did ($p = 0.04$).

Conclusions: Exposure to glucocorticoids prior to TAVR may be associated with reduced incidence of PPM requirement though larger studies are needed to support these findings. Tissue edema and inflammation may be significant contributors to the pathophysiology of conduction abnormalities after TAVR and could represent a therapeutic target.

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1. Introduction

Conduction abnormalities requiring permanent pacemaker (PPM) implantation continue to be a frequent problem following transcatheter aortic valve replacement (TAVR) [1,2]. PPM insertion following TAVR is a morbid complication associated with increased length of stay, blunted improvement in left ventricular ejection fraction, heart failure admissions, and possibly mortality [3,4]. The risk of conduction abnormalities following TAVR depends on patient, valve, and procedural characteristics [5]. While valve enhancements have improved in recent years and resulted in lower rates of paravalvular regurgitation, the incidence of PPM seems to be increasing [2]. Therefore, procedural and possibly pharmacological strategies to reduce the incidence of conduction abnormalities after TAVR are needed.

The TAVR prosthesis interacts with the conduction system in two possible ways. There can be direct mechanical damage of the conduction system by the radial force exerted by the TAVR prosthesis [6,7] and local tissue edema and fibrosis related to inflammation from the TAVR prosthesis and material used to seal PVL [8]. This second pathway could potentially be modified with the use of anti-inflammatory drugs prior to the procedure.

The aim of our study is to investigate if exposure to anti-inflammatory glucocorticoids prior to TAVR was associated with subsequent post-procedure conduction abnormalities and PPM insertion.

2. Methods

2.1. Patients

All patients undergoing TAVR at the Minneapolis VA Medical Center (Minneapolis, MN) between April 2015 and January 2017 and at the University of Minnesota Medical Center (Minneapolis, MN) between

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Table 1
Baseline and procedural characteristics.

	Steroids ($n = 16$)	No Steroids ($n = 151$)	p value
Age	76 (10)	80 (9)	0.07
STS median (IQR)	5.8 (3.9–7.9)	5.6 (3.1–8.8)	0.80
COPD (mod/severe)	(7) 43%	(28) 18%	<0.01
Home O2	(4) 25%	16 (10%)	0.09
Previous MI	(4) 25%	31 (21%)	0.30
Previous CABG	(5) 31%	33 (22%)	0.40
Atrial fibrillation	(7) 43%	49 (32%)	0.36
Right bundle brunch block	(1) 7%	21 (13%)	0.49
First degree AV block	(2) 12%	(16) 10%	0.81
Left anterior fascicular block	(0) 0%	(7) 4%	0.38
Intraventricular conduction delay	(0) 0%	(7) 4%	0.38
Transfemoral Access	(16) 100%	120 (80%)	0.07
Implantation Depth (mm, median-IQR)	4 (3.1–4.5)	4.4 (3.5–5.8)	0.28
Valve Type			
Sapien XT	7 (43%)	54 (36%)	0.58
Sapien 3	8 (50%)	79 (52%)	0.87
Corevalve/Evolut	1 (7%)	17 (12%)	0.55
Device Size			
23 mm	7 (43%)	23 (15%)	<0.01
26 mm	4 (25%)	54 (35%)	0.42
29 mm	5 (31%)	63 (41%)	0.43
31 mm	0	9 (6%)	0.31

November 2015 and November 2016 were included. Ascertainment of type and duration of exposure to glucocorticoids was retrospectively performed by linking electronic medical records to inpatient and outpatient pharmacy records. We excluded patients with prior left bundle branch block (LBBB) or prior PPM ($n = 32$) for a final sample size of 167 patients in this analysis. Baseline demographic and clinical information was recorded along with procedural outcomes. All patients were prospectively followed at 30-days post TAVR. Information relating to new conduction abnormalities or need for PPM insertion within the first 30 days following TAVR was prospectively captured in a dedicated database. The study was approved by the institutional review board at each institution.

2.2. Glucocorticoid exposure

Exposure to glucocorticoids was defined as receiving one dose of medication at least 1 day prior to, or on the day of, TAVR procedure. Any duration of treatment beyond one day was included in the exposure group. Administration could be oral or intravenous. Patients could be receiving glucocorticoids for any medically necessary indication.

2.3. TAVR procedure

All patients underwent careful evaluation prior to TAVR by a dedicated heart team consisting of cardiologists, interventional cardiologists, and cardiothoracic surgeons. Procedures were performed in a hybrid operating room under general anesthesia or conscious sedation. All patients received either the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA), Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, CA), Medtronic CoreValve (Medtronic Inc., Minneapolis, MN), or Medtronic Evolut (Medtronic Inc., Minneapolis, MN) prosthesis. Valve sizing was based on CT-derived area of the aortic annulus with additional information from echocardiographic and angiographic studies when necessary.

Primary end-point: The primary outcome was new PPM implantation within 30 days of the TAVR procedure. The decision to implant a PPM following TAVR was left up to the discretion of the heart team in consultation with cardiac electrophysiologists.

2.4. Statistical analysis

Continuous variables are presented as mean ± SD or as median with interquartile range. Categorical variables are reported as frequencies and percentages. Continuous variables were compared using the unpaired Student t-test or Mann–Whitney U test as appropriate. Discrete variables were compared with the chi-square test or Fisher exact test as appropriate. A 2-sided p value <0.05 was considered to be statistically significant. Medcalc® version 17.2 statistical software was used.

3. Results

A total of 167 patients were included in the study. The average age was 80 ± 9% and 80% of the patients were male. The mean Society of Thoracic Surgeons (STS) score was 6.6 ± 4.5%. Sixteen of the 167 patients (9.5%) were exposed to glucocorticoids prior to the index TAVR procedure. There were no baseline differences in STS score, atrial fibrillation, or right bundle branch block between those patients who received glucocorticoids and those who did not (Table 1). There were significantly more patients with moderate or severe chronic obstructive pulmonary disease (COPD) as well as patients requiring home oxygen in the glucocorticoid group (Table 1). The indications for glucocorticoids and their timing of administration in relation to TAVR are presented in Table 2.

The majority of patients underwent transfemoral TAVR (81.4%) with no significant difference between groups (Table 1). Most patients received either Edwards SAPIEN XT or Edward SAPIEN 3 valves, with fewer patients receiving Medtronic CoreValve or Medtronic Evolut There were no differences between groups in regard to which valve they received (Table 1). More patients in the glucocorticoid arm

Table 2
Duration, dose and clinical indication for glucocorticoid use.

	Steroid	Dose	Indication	Duration of exposure pre-TAVR
Patient 1	Hydrocortisone	100 mg q 8 h	Pulmonary fibrosis	1 day prior to TAVR
Patient 2	Prednisone	40 mg daily	COPD	16 days prior to TAVR
Patient 3	Prednisone	40 mg daily	COPD	>30 days
Patient 4	Prednisone	5 mg daily	Evan's syndrome	>30 days
Patient 5	Prednisone	40 mg twice daily	Contrast allergy	1 day prior to TAVR
Patient 6	Prednisone	40 mg twice daily	Contrast allergy	1 day prior to TAVR
Patient 7	Methylprednisolone	40 mg	Airway edema	1 day prior to TAVR
Patient 8	Prednisone	40 mg twice daily	Contrast allergy	1 day prior to TAVR
Patient 9	Prednisone	40 mg twice daily	Contrast allergy	1 day prior to TAVR
Patient 10	Prednisone	5 mg daily	Liver transplant	>30 days
Patient 11	Prednisone	10 mg daily	COPD	7 days prior to TAVR
Patient 12	Prednisone	5 mg daily	Kidney transplant	>30 days
Patient 13	Prednisone	5 mg daily	Eosinophilic syndrome	>30 days
Patient 14	Prednisone	5 mg daily	Lung transplant	>30 days
Patient 15	Prednisone	2.5 mg daily	Rheumatoid arthritis	>30 days
Patient 16	Prednisone	5 mg daily	COPD	>30 days

Table 3
Conduction abnormalities after TAVR according to exposure.

	Exposed to glucocorticoids (n = 16)	No exposure to glucocorticoids (n = 151)	*p* value
New pacemaker	0 (0%)	30 (19%)	0.04
High-degree (2nd or 3rd) block	0 (0%)	29 (19%)	0.05
New LBBB	3 (18%)	38 (25%)	0.57

received 23 mm valves than in the no glucocorticoid arm (43% vs 15%, $p < 0.01$). There were no other differences between groups in regard to valve size.

Overall 30 patients (18%) received a new permanent pacemaker within 30 days of the index TAVR procedure (Table 3). Indications for PPM implantation included high-degree AV block with either third degree AV block or Mobitz II AV block (19), new left bundle branch block [3], combination of high-degree AV block and new left bundle branch block [7], and new right bundle branch block [1]. None of the patients exposed to glucocorticoids required a permanent pacemaker (0%) while 30 (20%) of the unexposed patients did ($p = 0.04$). Similarly, more patients in the unexposed group developed new Mobitz II second- or third-degree heart block in the unexposed group when compared to the exposed group (0 (0%) vs 29 (19%), $p = 0.05$). There was no difference in new left bundle branch block between exposed (3, 18%) and unexposed patients (38, 25%), $p = 0.57$ (Table 3). Of note, all conduction abnormalities occurred within 24 h of the TAVR procedure. PPM implantation was performed within 3 days on all 30 patients.

4. Discussion

We evaluated the association between exposure to glucocorticoids prior to TAVR and subsequent conduction abnormalities and PPM insertion after the procedure. We found that patients exposed to glucocorticoids prior to TAVR were less likely to receive new PPM within 30 days of a TAVR procedure.

The development of conduction abnormalities following TAVR arises from factors related to patient, valve, and procedural characteristics [5]. Several pre-procedure predictors have been described including baseline conduction abnormalities, use of self-expanding prostheses, and the presence of calcium in the left ventricular outflow tract [3,5,9,10]. These risk factor suggest that the interplay of the TAVR prosthesis and the conduction system leads to conduction abnormality through the direct radial force the TAVR prosthesis exerts on the conduction system, and possibly tissue edema and fibrosis caused by the TAVR implant [6–8]. It is this second mechanism which could potentially be modified with the use of glucocorticoids given their anti-inflammatory and anti-edema properties [11]. Of note, many patients undergoing PPM implantation after TAVR are not pacemaker dependent during long-term follow-up suggesting a transient and perhaps reversible insult to the conduction system, such as myocardial edema, may be in part responsible for the conduction abnormalities seen shortly after the procedure [12]. It is unclear how rapidly the anti-inflammatory and anti-edema effects would occur in the heart and what effect long-term steroid use versus short-term dosing peri-procedurally would have on this process. Further studies would be required to investigate this further.

The use of glucocorticoids to prevent and treat conduction abnormalities related to transcatheter closure of ventricular septal defects has been studied previously with mixed results [13–15]. One prior study has examined exposure to glucocorticoids prior to TAVR and their effect on conduction abnormalities. Havakuk et al. studied 324 patients undergoing transfemoral TAVR who were pretreated with steroids ($n = 39$) due to either iodine allergy or active obstructive pulmonary disease [16]. Patients were treated with oral prednisone the day prior, and intravenous hydrocortisone the day of the TAVR. They found no difference in the primary composite outcome of new PPM or development of new conduction defects. The overall incidence of new conduction defects was 38% while the overall rate of new PPM was 25%. An important difference between the present study and Havakuk's is time of exposure to glucocorticoids. In our study, 10 out of 16 patients (62%) received steroids for >24 h prior to the procedure whereas in Havakuk's study exposure was limited to 1 day prior to the procedure. Exposure time could be an important variable to understand the anti-inflammatory efficacy of drugs with genomic effects like glucocorticoids [17].

Our paper has several important limitations including its retrospective nature, small sample size, and heterogeneity of baseline patient factors and steroid exposure. The small sample size and large treatment effects seen in this cohort may be due to chance. The small sample size also raises the question of whether numerical differences seen between groups in regard to baseline factors (younger age in the steroid group) or exposure (fewer self-expanding valves in the steroid group) are important despite not meeting statistical significance. The observed differences in outcomes may be due to the effect of measured and unmeasured confounders rather than corticosteroids. There is also heterogeneity in terms of the type of steroid used, dose, and length of exposure among patients that makes generalizability of our results difficult. Because of all these limitations, our results should be considered hypothesis-generating rather than confirmatory. Finally, there was no standardized process for deciding who would receive a PPM following TAVR and this was left to the discretion of the heart team with consultation from electrophysiology colleagues. In this study the majority of patients received PPM for high-grade AV block (26/30, 87%) though some received it for new isolated LBBB or even new RBBB with abnormal electrophysiological study. The optimal management of patients with LBBB after TAVR remains controversial and the degree of right ventricular (RV) pacing is highly variable (>40% pacing in 51% of patients) in TAVR patients [18]. Strategies to reduce RV pacing could be as beneficial and mitigate the deleterious effects of chronic RV pacing.

5. Conclusions

Exposure to glucocorticoids prior to TAVR is associated with a significant reduction in the rate of PPM at 30 days. Given the deleterious effect of ventricular pacing on clinical outcomes, a randomized clinical trial of glucocorticoids in high-risk patients may be warranted.

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