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Original Article

Comparison of subclinical neuronal injury by measuring neuron-specific enolase in patients with severe aortic stenosis treated with transcatheter aortic valve replacement or sutureless aortic valve replacement

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Abstract

Aim: Severe aortic valve stenosis (SAVS) which causes angina pectoris, syncope, arrhythmias, and sudden cardiac death, may be treated with transcatheter aortic valve replacement (TAVR) or sutureless aortic valve replacement (SU-AVR). We aimed to predict subclinical neuronal injury (SNI) by measuring neuron-specific enolase (NSE) in patients who underwent the TAVR and the SU-AVR.

Materials and Methods: This clinical trial was carried out between January 2015 and January 2017. A total of 53 patients who had severe aortic valve stenosis (SAVS) and underwent TAVR and SU-AVR were included. The Serum NSE level was measured just before and 24 hours after the procedure. Demographic variables, neurologic assessment findings, clinical and echocardiographic data, carotid ultrasounds reports, and laboratory findings were recorded.

Results: A total of 53 patients were included the study. The mean age was 78.4±8.6 and 20 were man (37.7%). The mean age of the TAVR group was significantly higher than the SU-AVR group (82.9±4.7 vs 71.5±8.7, p<0.001). The NSE level was significantly higher in the SUAVR group compared to the TAVR group after the procedure (21.15±10.25 vs 35.32±12.64, p<0.001). Differences between before and after the procedure the National Institutes of Health Stroke Scale (NIHSS), demographic and echocardiographic variables were similar between the two groups.

Conclusion: Serum NSE level was significantly higher in the SU-AVR group than the TAVR group Therefore, we may consider the SNI rate is higher as well. In patients who are at higher risk for neurological damage or have neurologic disease, TAVR may be a better treatment option instead of SUAVR.

Keywords: Neuron specific enolase (NSE); sutureless aortic valve replacement (SU-AVR); transcatheter aortic valve replacement (TAVR)

INTRODUCTION

Severe aortic valve stenosis (SAVS) is one of the most common heart valve diseases which causes narrowing aortic valve area and restricts blood flow from the left ventricle to the aorta. It may cause angina pectoris, syncope, arrhythmias, and sudden cardiac death. Patients who have SAVS are a candidate for aortic valve replacement due to the high mortality. After the symptoms begin, without the valve replacement, survival decreases dramatically. The successful treatment relieves symptoms and decreases mortality rate strikingly (1).

The stenotic aortic valve can be treated by a transcatheter approach which is called transcatheter aortic valve replacement (TAVR), or surgically. Open heart surgery is an effective and durable treatment of SAVS. If the Society of Thoracic Surgeons (STS) score is upper than 10, or logistic EuroSCORE is upper than 20, patients are accepted as high-risky for surgery and the TAVR is better option in these patients. The main complications of TAVR and surgery are stroke, vascular complications, and paravalvular regurgitation. In addition, pacemaker requirement is not uncommon complication in the TAVR group, unlike the surgery (2).

The new treatment method of SAVS is sutureless aortic valve replacement (SU-AVR). By the deployment of fewer than 3 locking sutures, it reduces the cardio-pulmonary bypass duration and cross-clamp time. Thus, provides

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better clinical outcome and is especially indicated in patients with multiple comorbidities who may benefit from reduced procedural times (3).

Neuron-specific enolase (NSE) is a neuronal cytoplasmic enzyme with a half-life of 48 hours (4). The level of NSE is found to be related to neuronal injury in several studies and may predict the size of neurological damage. The sensitivity and specificity of NSE in the diagnosis of neuronal injury were reported as 55% to 80% (5-7).

We aimed in this study, to investigate subclinical neuronal injury (SNI) by measuring the differences of increase of NSE in patients with SAVS who were performed TAVR and SU-AVR.

MATERIALS and METHODS

Study design

In this study, 65 consecutive patients presented with chest pain and shortness of breath and diagnosed with severe aortic valve stenosis were prospectively enrolled. Patients with malignancy, recent cerebrovascular accident, intracranial hemorrhage, head trauma, central nervous system tumor, degenerative central nervous system disorders, Gullian Barre syndrome, active infectious disease, neuroendocrine tumor, Creutzfeldt-Jakob disease, chronic kidney disease, chronic liver disease, peripheral arterial disease were excluded from the study. Patients developed procedure-related myocardial infarction, malign arrhythmias, aortic dissection were also not included. After excluding 12 patients who have various exclusion criteria, the study population consisted of 53 SAVS patients. NSE levels measured just before and 24 hours after the TAVR and the SU-AVR operations. Neurological and physical examinations were performed just before and 24 hours after as well. The neurological deficit was quantified by the use of the National Institutes of Health Stroke Scale (NIHSS). Neurological examination included the conscious statement, muscle strength, cerebellar examination, deep tendon reflexes, two-point discrimination, sensory of paint, and vibration.

Clinical and laboratory data assessment

Age, gender, height, and weight were obtained from the physical examination of patients. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters per participant. Vascular risk factors including hypertension, diabetes mellitus, hypercholesterolemia, and smoking status, and history of ischemic stroke were assessed. Society of Thoracic Surgeons (STS) scores, logistic Euro scores were calculated by web tools. Patients with blood pressure 140/90 mmHg or higher at 2 occasions or on antihypertensive medication were accepted as hypertensive. Diabetes mellitus was defined as fasting blood glucose > 126 mg/dL or patients on oral antidiabetic or insulin therapy (8). Hypercholesterolemia is accepted as fasting low-density lipoprotein (LDL) level > 160 mg/dL or total cholesterol > 200 mg/dL or patients on antihyperlipidemic therapy (9). The laboratory data included blood cell counts, fasting glucose, total cholesterol, LDL, urea, and creatinine. Transthoracic echocardiography was performed for each patient just before and after the procedures. Left atrial, left ventricular systolic and diastolic diameters and left ventricular ejection fraction (EF) were recorded. Patients with ejection fraction less than 40% were accepted as heart failure.

Neuron-specific enolase assessment

Before and 24 hours after the procedures blood samples were obtained and analyzed by Cobas 601 immunologic analyzer (Roche Diagnostic, Mannheim, Germany) and Elecsys NSE kits (Roche Diagnostics, Mannheim, Germany) with electrochemiluminescence immunoassay method. A level of NSE above 17.0 mg/dL was identified as positive according to the manufacturer's instructions.

Statistical analysis

The Statistical Package for the Social Sciences 21.0 statistical software program (SSPS Inc, Chicago, Illinois) was used for the statistical analysis. Continuous variables mentioned as the mean±standart deviation. Kolmogorov Smirnov test was used to check normality of continuous variables. Categorical variables mentioned as numbers and percentage. Student t-test and Mann-Whitney U test were performed to compare laboratory and clinical characteristics of patients as appropriate. Categorical characteristic of patients were compared by chi-square test. The paired sample t-test was performed to compare dependent variables and $p < 0.05$ was accepted as significant.

Ethics committee

All patients gave informed consent and study steps were approved by the ethics committee with the number/date of 23618724 / 11.11.2015.

RESULTS

Baseline characteristics were shown in Table 1. We included 53 patients consisting of 33 women (62.2%) and 20 men (37.8%) in our study. Thirty-two patients (60.4%) were performed TAVR and twenty-two patients (39.6%) were performed SU-AVR. The mean age of the TAVR group was 82.9±4.7 and of SU-AVR group was 71.5±8.7 (p=0.009). Characteristic features of patients including male gender (31.2% vs 47.6%, p=0.181), BMI (28 ± 5.4 vs 27.9 ± 4.9, p=0.181), hypertension (90.6% vs 80%, p=0.27), diabetes mellitus (37.5% vs 19%, p=0.13), smoking status (28.1% vs 28.5%, p=0.605), hyperlipidemia (53.1% vs 38%, p=0.215), the existence of congestive heart failure (25% vs 14.2%, p=0.28) were similar in both groups. None of the patients had acute or chronic kidney disease and the glomerular filtration rate was upper than 60 mL/min in each patient. Serum low density lipoprotein (LDL-C) (121.6±28.6 vs 121.4±33.9, p=0.979), total cholesterol (184.8±38.7 vs 197.8±48.3, p=0.284), triglyceride (131.5±71.7 vs 117.7±43.9, p=0.436) were similar in TAVR and SU-AVR groups. LV ejection fraction (52.8±11.4 vs 58.1±10, p=0.091) and mean gradient of the aortic valve (50.6±21.5 vs 42±11.9, p=0.067) also were

similar between TAVR and SU-AVR groups. Preoperative (0.59±0.61 vs 0.62±0.59, p=0.882) and postoperative (1.1±0.9 vs 1.3±0.7, p=0.286) NIHSS scores were similar in both groups. Only one patient in each group had unilateral carotid artery disease without significant narrowing (0.3% vs 0.4%, p=0.1)

Preoperative NSE level was higher in SU-AVR group than TAVR group (13.67±7.03 vs 10.6±3.8, p=0.039). Postoperative NSE level was also higher in SU-AVR than TAVR group (35.32±12.64 vs 21.15±10.25, p<0.001). NSE level was increased in both TAVR group (10.06±3.8 vs 21.16±10.25, p< 0.001) and SU-AVR group (13.69 ± 7.03 vs 35.32 ± 12.64 ; p< 0.001). (Table 1, Figure 1a, and 1b). It was significantly higher the amount of increase of the NSE level in the SU-AVR group compared to the TAVR group (21.62±12.82 vs 11.09±9.1, p<0.001) (Table 1, Figure 2).

Table 1. Clinical and laboratory characteristics of the study population

	TAVR (n = 32)	SU-AVR (n = 21)	All patients (n=53)	P-value
Age, years	82.9±4.7	71.5±8.7	78.4±8.6	0.009
Gender (male), n (%)	10 (31.2%)	10 (47.6%)	20 (37.7%)	0.181
BMI, kg/m²	28±5.4	27.9±4.9	28±5.2	0.931
Hypertension, n (%)	29 (90.6%)	17 (80%)	46(86%)	0.27
Diabetes mellitus, n (%)	12 (37.5%)	4 (19%)	16(30%)	0.13
HL, n (%)	17 (53.1%)	8 (38%)	25(47.1%)	0.215
GFR, mL/min/1.73 m²	95.2±34.3	118.2±28.4	104.3±33.7	0.153
Smoking, n (%)	9 (28.1%)	6 (28.5%)	15(28%)	0.605
UICAO, n (%)	1 (0.3%)	1(0.4%)	2(0.3%)	> 0.1
CHF, n (%)	8 (25%)	3 (14.2%)	11(20.7%)	0.28
LVEF, %	52.8±11.4	58.1±10	54.9±11.1	0.091
Mean gradient, mmHg	50.6±21.5	42±11.9	45.4±16.7	0.067
Total cholestrol, mg/dL	184.8±38.7	197.8±48.3	189.9±42.8	0.284
Tryglicerides, mg/dL	131.5±71.7	117.7±43.9	126.1±60.1	0.436
LDL cholestrol, mg/dL	121.6±28.6	121.4±33.9	121.5±30.5	0.979
Preoperative NSE, ng/mL	10.6±3.8	13.67±7.03	11.5±5.5	0.039
Postoperative NSE, ng/mL	21.15±10.25	35.32±12.64	26.7±13.1	< 0.001
Difference of NSE, ng/mL	11.09±9.1	21.62±12.82	15.26±11.82	<0.001
Preoperative NIHSS	0.59 ± 0.61	0.62 ± 0.59	0.6±0.6	0.882
Postoperative NIHSS	1.1± 0.9	1.3± 0.7	1.2±0.8	0.286

BMI: Body mass index, HL: Hyperlipidemia, GFR: Glomerular filtration rate, CHF: Chronic heart failure, UICAO: Unilateral internal carotid artery obstruction, BICAO: Bilateral internal carotid artery obstruction, LDL: Low density lipoprotein, LVEF: Left ventricular ejection fraction, NSE: Neuron specific enolase, NIHSS: National Institutes of Health Stroke Scale

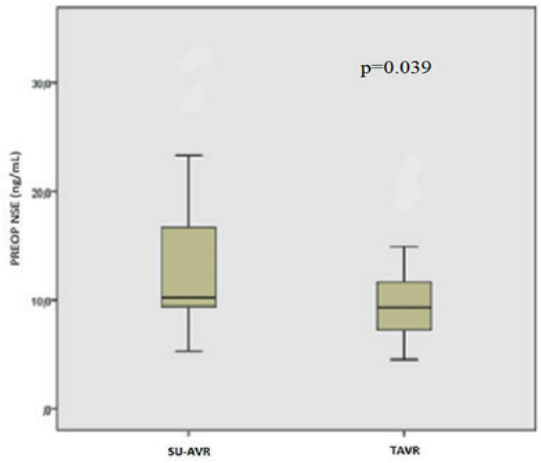

Figure 1a. Preoperative NSE levels of TAVR and SU-AVR patients

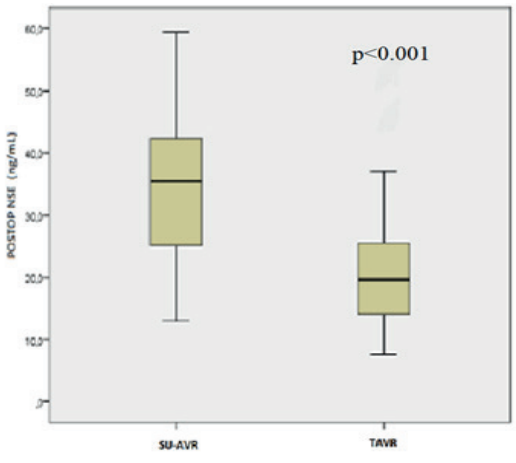

Figure 1b. Postoperative NSE levels of TAVR and SU-AVR patients

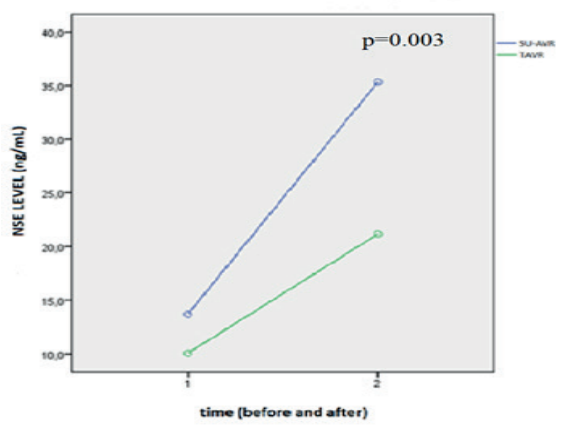

Figure 2. Amount of increase of NSE levels in TAVR and SU-AVR groups

DISCUSSION

We found that the NSE level was higher in patients underwent SU-AVR compared to TAVR. This study is the first investigating the neurological influence of TAVR and SU-AVR.

Patients who have symptoms such as angina pectoris, shortness of breath, and syncope are needed to treat due to they have a high mortality rate without treatment. In general, pharmacotherapy is not adequate to release the symptoms of SAVS. Interventional therapy, including TAVR and open-heart surgery, are proven procedures for improving the quality and duration of life (1,2).

Stroke is one of the major complications of TAVR and open-heart surgery. It was thought that neuronal injury was raising up in the TAVR group from a blood clot and in the surgery group from hypoperfusion. Although neurological damage had been seen higher in the TAVR group compared to surgery group, we need further research due to the conflicting results. (3,10) However, SU-AVR is expected to have better outcomes, studies have shown similar neurological events rates in SU-AVR and TAVR groups (11,12).

In PARTNER trials TAVI patients had a higher neurological event rate compared to open-heart surgery at 30 days and in 1 year follow up. Afterward, this rate linked to patient-related factors regardless of the operation type up to 2 years. The cause of this lower rate of the neurological event in the surgery group was thought to be related to the removal of the deformed and calcified native valve from the aortic root. In TAVR patients, to avoid the microembolisms, it was suggested to use new devices (13,14). In another study, it was found that new foci of restricted diffusion in Diffusion-Weighted Magnetic Resonance Imaging (DW MRI) were detected in 84% of patients who underwent TAVR. This rate was 48% in patients who underwent surgery and these all findings were clinically silent at 3 months (15). These results were compatible with the PARTNER trials as it showed that the early phase neurological damage rate was higher in the TAVR group than the surgery group. Contrary to these findings, neurologic event rates after TAVR were demonstrated a decrease from 7% to 1.7– 4.8% in recent studies. These inconsistent results led to speculated that SAVR related neurological events were not well-reported previously and real incidence of stroke was higher than noticed (16,17). Detailed and standardized neurological assessments were missing due to the uniform neurological definitions by neurologists in the majority of studies evaluating neurological assessment after SAVR. This was apparent in Messe's prospective trial: 34 strokes were detected in 196 patients undergoing SAVR (17%), but only 13 of these have been reported in the STS Database (6.6%) (18).

The new technique of surgery, SU-AVR has been developed which is a less invasive option. It refrains the placement of sutures to the aortic root (19). The sutureless valve prostheses need not more than three locking sutures to deploy to aortic root adequately. This provides shorter cardiopulmonary bypass and aortic cross-clamp time (20). Besides, by providing shorter CPB and aortic cross-clamp duration and likely with decalcification, reduced brain microembolisms were seen in comparison to TAVR (21). However, current studies showed that SU-AVR has similar mid-term outcomes and neurological events rate with TAVR, but, there are still inconsistent findings in some studies and we need further investigation (22,23).

However, magnetic resonance imaging (MRI) is the gold standard technique to detect the SNI in patients with suspicious for SNI, but it is expensive, time-consuming, and not always available. Therefore its use as a routine screening tool is limited. For this purpose, a blood biomarker of SNI is suggested in daily clinical practice. One of these blood tests is the NSE (24). It is well known that the NSE level is related to neurological events. Many studies showed the serum concentrations of NSE has a high predictive value for early and late neurobehavioral outcomes after the acute stroke, cardiac arrest, cardiopulmonary bypass, and other cardiac surgeries (25-27). Decreased NSE level in time was found to be related to reduced neuronal death treated by hypothermia in patients with cardiac arrest (28). Another study conducted with cardioverter-defibrillator implanted patients showed the NSE level was related to neurocognitive function (29).

LIMITATIONS

A small number of the study population is the first limitation of our study. The second is the limited follow-up period of patients. Serial measurements of NSE and long term follow-up might be facilitated to predict SNI. The NSE level could be supported by DW MRI. The anesthetic burden was ignored in the SU-AVR group.

CONCLUSION

In conclusion, the NSE level may be utilized to evaluate SNI in patients who underwent interventional treatment for SAVS. However, we do not have proof of stroke in our patients after the SU-AVR procedure, but we may speculate that the SNI rate may be much more in the SU-

AVR than the TAVR group. Post-procedural following of NSE levels may guide to estimate neurological progress. We need further study to evaluate SNI adequately though. In patients who have a predisposition of neurological damage or neurologic disease, or with older age, TAVR could be a better option instead of SU-AVR.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: All patients gave informed consent and study steps were approved by the ethics committee of Kanuni Health Sciences Education and Research Hospital in Trabzon with the number/date of 23618724 / 11.11.2015.

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