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Dexmedetomidine for transcatheter aortic valve implantation. Does it protect against acute kidney injury?

Dexmedetomidina en el implante de válvula aórtica transcatéter.
¿Protege frente a la insuficiencia renal aguda?

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a frequent complication after transcatheter aortic valve implantation (TAVI), and it presents a higher risk of myocardial infarction, severe bleeding, transfusion, dialysis, and mortality. Dexmedetomidine has a protective effect on AKI after adult cardiac surgery. We want to study the impact of dexmedetomidine on the incidence of AKI in the postoperative period of TAVI procedure in our center. **Methods:** We performed a retrospective cohort study comparing the administration of dexmedetomidine (DEX group) versus other sedatives (NO-DEX group) during elective TAVI procedure under transfemoral approach. **Results:** A total of 122 patients were included in the study. Both groups presented a similar incidence of AKI (19,8% DEX group; 19,2% NO-DEX group; $p = 0,949$). A subgroup analysis with patients presenting chronic kidney disease showed an AKI incidence of 24%, without statistically significant differences between both groups either. **Conclusions:** We did not find any difference on AKI incidence, length of hospital stay, 30-day mortality or 12-month mortality in patients undergoing TAVI procedure under sedation with dexmedetomidine compared to other sedatives in our center. It would be interesting to study this hypothetical association through studies with larger samples and better designs.

Key words: Dexmedetomidine, conscious sedation, acute kidney injury, transcatheter aortic valve implantation.

RESUMEN

Introducción: La insuficiencia renal aguda (AKI) es una complicación frecuente tras el implante de válvula aórtica transcatéter (TAVI), y presenta un mayor riesgo de infarto agudo de miocardio, sangrado severo, transfusión, diálisis y mortalidad. La dexmedetomidina presenta un efecto protector sobre AKI tras cirugía cardíaca en el adulto. Queremos estudiar el impacto de la dexmedetomidina en la incidencia de AKI en el posoperatorio de procedimiento TAVI en nuestro centro. **Métodos:** Hemos realizado un estudio de cohorte retrospectiva comparando la administración de dexmedetomidina (grupo DEX) frente a otros sedantes (grupo NO-DEX) durante el procedimiento TAVI electivo con abordaje transfemoral. **Resultados:** Se incluyeron en el estudio un total de 122 pacientes. Ambos grupos presentaron una incidencia similar de AKI (19,8% el grupo DEX; 19,2% el grupo NO-DEX; $p = 0,949$). En un análisis de subgrupo en pacientes con insuficiencia renal crónica mostró una incidencia del 24% sin diferencias estadísticamente significativas entre ambos grupos tampoco. **Conclusiones:** No hemos encontrado ninguna diferencia en la incidencia de AKI, duración de estancia hospitalaria, mortalidad a 30 días y mortalidad a 12 meses en pacientes intervenidos de TAVI bajo sedación con dexmedetomidina comparada con otros sedantes en nuestro centro. Sería interesante estudiar esta hipotética asociación mediante estudios con muestras mayores y mejor diseñados.

Palabras clave: Dexmedetomidina, sedación consciente, insuficiencia renal aguda (AKI), implante de válvula aórtica transcatéter (TAVI).

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Introduction

The main indication for transcatheter aortic valve implantation (TAVI) is the severe aortic stenosis in a calcified tricuspid valve in high-risk surgical patients. It is also a therapeutic option for severe aortic insufficiency, severe aortic stenosis in a bicuspid valve, bioprosthetic valve dysfunction, and the clinical decision-making should be assessed by the multidisciplinary Heart Team[1].

Patients undergoing a TAVI procedure can suffer from several cardiovascular complications in the perioperative period that require a close surveillance for an early diagnosis and treatment, if required[2],[3]. Acute kidney injury (AKI) is a frequent complication with an estimated incidence of 22,1%, with differences among studies that could be explained by the presence of varied diagnostic criteria, while the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classification systems are the ones recommended by the Valve Academic Research Consortium-2 (VARC-2)[4],[5]. Patients who suffer from AKI in the postoperative period of TAVI present a higher risk of myocardial infarction, severe bleeding, transfusion, dialysis and mortality[6].

TAVI procedure involves the administration of contrast media, hypotensive episodes during rapid pacing, preoperative volume depletion and catheter manipulation in the aorta of patients with atherosclerosis and risk of embolization. All of these are risk factors associated with AKI[3],[7].

Several other risk factors for AKI after TAVI procedure were identified: transapical approach, chronic kidney disease, class IV of the New York Heart Association (NYHA) classification, peripheral artery disease, atrial fibrillation, congestive cardiac failure, diabetes mellitus, red blood cell transfusion, postoperative thrombocytopenia, systemic inflammatory response syndrome, hypertension, stroke and chronic obstructive pulmonary disease (COPD)[8],[9],[10],[11].

TAVI procedure is usually performed under general anesthesia or under sedation along with local anesthesia. Patients undergoing sedation with local anesthesia need a lower amount of inotropic agents and a shorter intensive care unit stay than those under general anesthesia, but both techniques show similar complication rates and mortality. For this reason, the current scientific evidence does not support one technique over another[12],[13].

Dexmedetomidine is an alpha-adrenergic agonist with sedative, analgesic and opioid-sparing effects and it is indicated for sedation in critical care units and for procedural sedation[14],[15]. Dexmedetomidine has a protective effect on AKI after adult cardiac surgery[16],[17] and it is safe in adults > 65

years[18]. Both propofol and dexmedetomidine are appropriate sedatives for TAVI procedures, as observed in comparative studies[19],[20].

We want to study the impact of dexmedetomidine on the incidence of AKI in the postoperative period of TAVI procedure in our center.

Methods

We performed a retrospective cohort study comparing the administration of dexmedetomidine (DEX group) versus other sedatives (NO-DEX group) during elective TAVI procedures under transfemoral approach between January 2019 and May 2020 in Virgen de la Victoria University Hospital, Spain.

To design an adequate sample recruitment, the period of time selected for the study owes to changes in both the technique of the TAVI procedure and the usual anesthetic management for these interventions in our center. In January 2019 the Cardiology Department begun to use the new-technology recapturable valve prosthesis, and this also conditioned a contrast dose reduction. Also, in the recent years, dexmedetomidine started to be available in our center and, since May 2020, most TAVI procedures are being performed under dexmedetomidine-based sedation regimens owing to the anesthesiologists' preference.

The main outcome was the incidence of AKI in the first 7 postoperative days. Secondary outcomes were the length of postoperative hospital stay, 30-day mortality and 12-month mortality.

Exclusion criteria were: stage 5 chronic kidney disease, urgent procedure, acute heart failure, other than transfemoral approach and those in which general anesthesia was the anesthetic plan from the beginning.

Data of the patients included in the study were collected from the digital medical records. We studied several variables: age, sex, weigh, height, obesity according to body mass index, length of hospital stay, chronic kidney disease, baseline creatinine, hypertension, diabetes, NYHA functional class, stroke, atrial fibrillation, left ventricular ejection fraction, American Society of Anesthesiology (ASA) Physical Status classification system, contrast media volume, sedative drugs during the procedure, perioperative complete atrioventricular block, perioperative need for red blood cell (RBC) transfusion, perioperative definitive pacemaker implantation, need for vasoactive drugs, intensive care unit (ICU) admission, extracorporeal kidney-replacement therapy, the develop of AKI according to VARC-2 criteria (Table 1), 30-day mortality, 12-month mortality and

Table 1

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in Cr > 0.3 mg/dL OR >150%-200% from baseline	< 0.5 mL/kg/h for > 6h
2	Increase in Cr > 200%-300% from baseline	< 0.5 mL/kg/h for >12h
3	Increase in Cr > 300% from baseline OR Cr of > 4.0 mg/dL, with increase > 0.5 mg/dL	< 0.3 mL/kg/h for 24 h OR Anuria for 12 h

conversion to general anesthesia.

Chronic kidney disease was considered in case it was previously diagnosed or whether a baseline glomerular filtration rate $< 60 \text{ ml/min/1.73 m}^2$ was detected in the digital medical records. The preoperative baseline creatinine was established as the one upon hospital admission or that after preoperative treatment and recovery of any medical condition present at hospital admission.

The information was processed and analyzed with IBM SPSS Statistics 24. Several descriptive statistics were used: mean, median, mode, quartiles, and percentiles. We also needed different analytical statistics. Comparison between numerical variables showing a normal distribution was performed using the Student's t-test, while those presenting a non-normal distribution were analyzed with the Mann-Whitney U test after checked with the Kolmogorov-Smirnov test for normality. We used the Chi-squared test to check the independence of two categorical variables, and the Fisher test was used in case the sample size was small. A value of $p < 0,05$ was considered statistically significant.

Results

A total of 122 patients were included in the study (96 belonging to DEX group and 26 to NO-DEX group). Both groups were similar in terms of age, sex, obesity, hypertension, dia-

betes mellitus, atrial fibrillation, class IV of the NYHA, stroke, amount of contrast media and conversion to general anesthesia (Table 2).

Preoperative physical status was ASA-IV in the 42.6% of the whole sample, and the rest of them were ASA-III. Only seven patients (5.3%) in the sample had a severely reduced left ventricular ejection fraction (LVEF $< 35\%$), all of whom were included in the DEX group. The incidence of complete atrioventricular block in the sample was 19.7%, and 13.1% of the patients in the sample received a pacemaker implantation in the postoperative period. Vasoactive drugs were needed in 26.2% of the patients in the sample. Admission to the ICU was necessary in 21 (17.2%) patients in the sample.

Prevalence of ASA-IV, severely reduced left ventricular ejection fraction, incidence of complete atrioventricular block, pacemaker implantation, the need for vasoactive drugs, and ICU admission were higher in the DEX group, but these differences were not statistically significant. Perioperative RBC transfusion was administered in 40.2% of the patients, with a non-significant higher incidence in the NO-DEX group.

Dexmedetomidine was always combined with remifentanyl, and 41% of patients also received low-dose ketamine. The NO-DEX group was sedated with propofol alone in 58% of cases and different combinations of propofol with midazolam, remifentanyl, fentanyl and ketamine were used in the rest of the cases. Only a single patient, who was included in the DEX group, needed conversion to general anesthesia in the context

Table 2. Patient characteristics

	Dex (n = 96)	No dex (n = 26)	p-value
Preoperative			
Age +	79.4 \pm 7.1	80.7	0.554
Sex (M:F, n)	44:52	8:18	0.168
IMC (kg/m ²) +	28.4 \pm 4.8	28.6 \pm 4.1	0.881
Obesity	27 (35.5%)	7 (30.4%)	0.652
Hypertension	83 (86.5%)	24 (92.3)	0.420
Diabetes mellitus	34 (35.4%)	10 (38.5%)	0.774
Atrial fibrillation	27 (28.1%)	5 (19.2)	0.360
NYHA grade IV	12 (12.5%)	5 (19.2%)	0.379
Cerebrovascular disease	12 (12.5%)	2 (7.7)	0.495
FEVI $< 35\%$	7 (7.3%)	0 (0%)	0.344
Chronic kidney disease	39 (40.6%)	11 (42.3%)	0.877
ASA 4	45 (46.9%)	7 (26.9%)	0.068
Perioperative			
Contrast amount (ml) +	143.8 \pm 52.4	152.2 \pm 52.1	0.491
Auriculoventricular block	21 (21.9%)	3 (11.5%)	0.240
Definitive pacemaker need	14 (14.6%)	2 (7.7)	0.518
Conversion to general anesth	1 (1%)	0 (0%)	1
Red blood cells transfusion	37 (38.5%)	12 (46.2%)	0.482
Admission at ICU	19 (19.8%)	2 (7.7%)	0.240
Vasopressor drugs usage	29 (30.2%)	3 (11.5%)	0.055

Data is expressed as n (percentage)/ +: mean \pm SD / Statistical significance established as $p < 0.05$.

Table 3

Outcomes	Dex (n = 96)	No dex (n = 26)	p-value
Acute kidney injury	19 (19.8%)	5 (19.2%)	0.949
Length of hospital stay β	4 [4-6]	3 [3-4.5]	0.233
30-day mortality	1 (1%)	1 (3.8%)	0.382
12-month mortality	12 (12.5%)	3 (11.5%)	1

Data is expressed as n (percentage) / β: median [interquartile range] / Statistical significance established as $p < 0.05$.

of accidental femoral artery dissection during the procedure. This patient required a vascular repair for which local anesthetic infiltration could not provide enough analgesia. This difference did not reach statistical significance.

Only 24 patients (19.7%) suffered from AKI in the postoperative period (Table 3).

Except for one patient who presented AKI-II (NO-DEX group), the rest of the patients had the lowest degree of kidney dysfunction, AKI-I. None of the patients required extracorporeal kidney-replacement therapy in the postoperative period. Both groups presented a similar incidence of AKI (19.8% DEX group; 19.2% NO-DEX group; $p = 0.949$). A subgroup analysis with patients presenting chronic kidney disease showed an AKI incidence of 24%, without statistically significant differences between both groups (25.6% DEX group; 18.2% NO-DEX group; $p = 1$).

The postoperative hospital length of stay in our sample had a median of three days, corresponding to 47.5% of the patients. The minimum length of stay was two days, and the maximum was 20 days. In 75% of the patients in the sample the length of stay was five days or less. Median hospital length of stay in the NO-DEX group was lower than the DEX group, with a non-significant statistical difference.

Only two patients (each of them belonging to a different group) died in the first 30 postoperative days, corresponding to a mortality of 1.6% in the sample, without differences between the two groups. A patient in the DEX group died in the immediate postoperative period in the context of acute pulmonary oedema. The other patient, belonging to the NO-DEX group, died on the sixth postoperative day in the ward in the context of AKI-II. In the first postoperative year, a sum of 15 patients (12.3%) died, without differences between the two groups.

Discussion

A meta-analysis of randomized controlled trials concluded that perioperative administration of adult patients undergoing cardiac surgery may reduce the incidence of postoperative AKI[16]. Recently, another randomized controlled trial regarding the impact of dexmedetomidine on AKI in the postoperative of adult aortic surgery showed a protective effect of this sedative on kidney function along with a reduction on length of hospital stay, without any significant increase of side effects[17]. Contrary to what we expected, in our study we have not observed any difference on AKI incidence when using dexmedetomidine in the perioperative of TAVI under sedation. Moreover, we have not identified any differences on length of hospital stay, 30-day mortality or 12-month mortality. We could not find any paper

studying the influence of dexmedetomidine on perioperative kidney function in TAVI procedures, so our investigation would probably be the first one on this topic.

In our study, the DEX group had a higher prevalence of ASA-IV physical status and severely reduced left ventricular ejection fraction, and although these differences did not reach the statistical significance, it seems that the anesthesiologists were prone to choose a dexmedetomidine-based sedation for patients with higher comorbidity.

Incidence of AKI in our study was 19.7%, which is slightly lower than the incidence of 22.1% reported in a recent meta-analysis on AKI in patients undergoing TAVI procedures. Of note, except for a patient who suffered from AKI-II, the rest of the patients presented the least severity of kidney dysfunction, corresponding to an AKI-I. While the meta-analysis showed a 5.8% incidence of extracorporeal kidney-replacement therapy, in our sample none of the patients needed it[6].

Recently, the marketing authorisation holders for dexmedetomidine-containing products in agreement with the European Medicines Agency informed an increased risk of mortality in ventilated critically ill adult ICU patients under sedation with dexmedetomidine in the age group ≤ 65 years compared with alternative sedatives[22]. This warning was based on SPICE III, a randomized controlled trial which also reported a 90-day mortality reduction in ventilated critically ill ICU adult patients under sedation with dexmedetomidine in the age group > 65 years compared with alternative sedatives[18]. In our study, 95% of patients were > 65 years and 12-month mortality was 12.5%, without any difference between the groups, and this involves a lower rate of that found (17.8%) in other studies about TAVI procedures[23].

We did not find any difference between the groups regarding the incidence of conversion to general anesthesia, and the only patient who needed it was owing to a surgical complication.

It would be interesting to study an hypothetical influence of dexmedetomidine on the development of complete atrioventricular block during TAVI procedure, as we found a higher incidence in the DEX group with a non-significant statistical difference. It is possible that an additive effect between the mechanical compressive effect of the implanted bioprosthetic aortic valve and the pharmacological depressant effect of dexmedetomidine on the atrioventricular node could increase the risk of complete atrioventricular block. As far as we know, this has not been studied before.

Our study presents some limitations. The sample size is reduced, specially the NO-DEX group, as the recruitment is limited by the technical change in TAVI procedures and the anesthesiologists' sedation regimen preferences, as detailed in the

methods section. This could involve a low statistical potency to detect any possible association between dexmedetomidine and kidney function and also the secondary outcomes: length of hospital stay, 30-day mortality and 12-month mortality.

Owing to the continuous surveillance needed during TAVI procedures, the recording of vasoactive drugs in the anesthesia record sheets is sometimes incomplete, which could influence the data collection. Also, the lack of systematic measurement of the urine output in the ward limited the diagnostic criteria of AKI, so serum creatinine was the only criteria used. Finally, this is a retrospective study and, as such, it presents the intrinsic limitations of this kind of study.

Conclusions

We did not find any difference on AKI incidence, length of hospital stay, 30-day mortality or 12-month mortality in patients undergoing transfemoral TAVI procedure under sedation with dexmedetomidine compared to other sedatives in our center. It would be interesting to study this hypothetical association through studies with larger samples and better designs.

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