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Original Research Article

ORIGINAL RESEARCH ARTICLE

Impact of perioperative dexmedetomidine treatment on 1-year mortality in patients undergoing orthotopic heart transplantation

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Abstract

Background: Heart transplantation remains the gold standard treatment of end stage heart failure. The prognosis of heart transplantation has continuously improved, with a 10-yr survival of 53%. Dexmedetomidine is commonly used as a sedative in cardiac patients. Recently its clinical use has been limited because it was associated with increased mortality in the SPICE 3 trial. The impact of perioperative dexmedetomidine treatment on patients undergoing heart transplantation has not been examined yet. Therefore, this study investigated the influence of dexmedetomidine treatment on 1-yr mortality in patients undergoing heart transplantation.

Methods: This retrospective cohort study included patients who underwent heart transplantation at the University Hospital Duesseldorf between 2011 and 2021. The main exposure was perioperative dexmedetomidine treatment. The primary endpoint was 1-yr mortality after surgery. Kaplan–Meier analysis and multivariate cox regression with adjustment for risk index for mortality prediction after cardiac transplantation (IMPACT) and packed red blood cells were performed.

Results: A total of 267 patients were screened. To avoid a potential selection bias, patients who needed postoperative treatment with extracorporeal life support system were excluded, leaving 169 patients included in the analysis. Out of 169 patients, 85 received perioperative dexmedetomidine treatment and 84 were not treated with dexmedetomidine. Overall, 1-yr mortality was 10.3% (dexmedetomidine 4.9% *vs* no dexmedetomidine 15.5%, $P=0.025$). After adjustment for IMPACT score and packed red blood cells, dexmedetomidine treatment was independently associated with lower 1-yr mortality after heart transplantation (hazard ratio: 0.25, 95% confidence interval 0.07–0.93, $P=0.03$).

Conclusion: Perioperative dexmedetomidine treatment appears to be safe regarding 1-yr mortality in patients undergoing orthotopic heart transplantation.

Keywords: 1-year mortality; dexmedetomidine; heart failure; heart transplantation; IMPACT-score

For patients with end-stage heart failure, heart transplantation (HTX) remains the gold standard therapy.[1,2] The highly selective alpha-2-agonist dexmedetomidine (Dex) is commonly used as a sedative in cardiac surgery patients.[3] Results from a meta-analysis indicate a reduction in short-term mortality along with decreased duration of tracheal intubation and ICU stay after cardiac surgery.[4] However, in 2019 Shehabi and colleagues[5] published results from the randomised 'The Sedation Practice in Intensive Care Evaluation' (SPICE) III trial, comparing the early use of Dex as primary sedative in

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mechanically ventilated patients on the ICU.[5] While there was no difference in overall mortality between Dex and usual-care treatment, an age-related subgroup analysis reported a higher mortality in patients under the age of 65 yr in the Dex group. These results led to a restriction in the clinical use of Dex. To this day there are no data on Dex exposure and mortality in patients after HTX. The aim of this retrospective cohort study was to investigate a potential influence of perioperative Dex-based sedation after HTX on 1-yr mortality.

Methods

This retrospective single-centre cohort study was approved by the University of Duesseldorf's ethics committee (approval number: 2022−2016; approval date: 25 October 2022; study title: 'Perioperative effect of Dexmedetomidine on patients undergoing HTX − a retrospective cohort study'). It was carried out in compliance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1975. Data were extracted from the local HTX database and electronic medical charts using standard definition by trained personnel. All patients had given written informed consent to be registered in this database. Reporting of this work corresponds to the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines.[6]

This study included all patients aged ≥18 yr who underwent HTX at the University Hospital Duesseldorf, Germany between 2011 and 2021. A requirement for extracorporeal life support system (ECLS) led to exclusion. Further, patients with missing data regarding sedative treatment or mortality were excluded from the analysis. The main exposure was perioperative Dex-based sedation during surgery and up to 72 h after HTX. The primary outcome was mortality at 1 yr after HTX. The main covariable was the validated index for mortality prediction after cardiac transplantation (IMPACT) and perioperative red blood cell transfusion.[7,8]

Statistical analysis

Statistical analysis was performed using IBM SPSS© software version 27.0 (Armonk, NY, USA). Continuous variables were presented as mean and standard deviation (SD). Categorical variables were presented as numbers (*n*) with corresponding percentages (%). For analysis of the primary endpoint, survival analysis was performed by cox regression and Kaplan−Meier analysis. In line with the widely used 'rule of thumb' one variable per 10 events was included in the multivariable analysis. The continuous IMPACT score was calculated using preoperative recipient risk factors (age, serum bilirubin, creatinine clearance, dialysis, sex, heart failure aetiology, preoperative infection, race, circulatory support, and type of ventricular assist device). For all statistical tests, a *P*-value <0.05 was considered significant.

Results

Study cohort and characteristics

Between 2011 and 2021 a total of 267 patients underwent HTX at the University Hospital Duesseldorf; 84 patients needed postoperative ECLS treatment and 18 had missing data for the primary endpoint and were excluded from analysis. Among the 169 included patients (mean age 55 SD=11 yr), 85 were exposed to perioperative Dex-based sedation while 84 were not treated with Dex at any time. Patients in the Dex group were older compared with patients without Dex treatment (Dex 57 [SD = 11] yr *vs* no Dex 52 [SD=12] yr, *P*=0.01). There was no difference in baseline and surgery characteristics between the groups (Table 1), nor in the preoperative IMPACT score (Dex 8.3 [SD=4.0] *vs* no Dex 7.7 [SD=4.1], *P*=0.353). Patients in the no Dex group received significantly more packed red blood cells (PRBCs) (no Dex 15 [SD=13] *vs* Dex 10 [SD=6], *P*<0.001). We calculated the vasoactive-inotropic score (VIS) as a weighted sum of all administered inotropes and vasoconstrictors during the ICU stay. VIS was higher in patients in the no Dex group (no Dex 32.5 [SD=12.6] *vs* Dex 26.2 [SD=13.8], *P*=0.02). During the first year after HTX, a total of 17 patients (10.3%) died (Dex *n*=4 [4.9%] *vs* no Dex *n*=13 [15.5%]).

Perioperative Dex treatment

A total of 85 patients were treated with Dex as the primary sedative on the ICU with a mean dose of 1.1 (SD=0.5) $\mu g\ kg^{-1}\ min^{-1}$ (Table 2). A total of 36 patients were also treated with Dex during HTX with a mean dose of 0.9 (SD=0.3) $\mu g\ kg^{-1}\ min^{-1}$. In these patients Dex was started at skin incision and was also used for sedation on the ICU. Overall, patients were treated with Dex for a total of 29 (SD=20) h.

Perioperative Dex treatment and 1-year mortality

Kaplan−Meier analysis showed a significant difference in 1-yr mortality between Dex and no Dex patients (Fig 1, *P*=0.03). A Cox regression model detected a significantly higher hazard for 1-yr mortality in patients not exposed to Dex compared with patients receiving Dex-based sedation (hazard ratio [HR]: 3.34, 95% confidence interval [CI] 1.09−10.25, *P*=0.04). There was no influence of age on 1-yr mortality in our study cohort (HR: 1.04, 95% CI 0.99−1.10, *P*=0.12). Further, neither the mean dose (HR: 0.25, 95% CI 0.02−3.81, *P*=0.32) nor the duration of Dex treatment (HR: 0.88, 95% CI 0.78−1.03, *P*=0.12) was associated with outcome after HTX. We did not detect an impact of vasoactive-inotropic support on 1-yr mortality (HR: 1.02, 95% CI 1.0−1.05, *P*=0.084). The amount of PRBCs showed an association for 1-yr mortality in univariate analysis (HR: 1.04, 95% CI 1.02−1.06, *P*<0.001). After adjustment for IMPACT score and PRBCs, perioperative Dex treatment remained independently associated with lower 1-yr mortality (HR: 0.25, 95% CI 0.07−0.93, *P*=0.03) (Table 3).

Discussion

Results from this study suggest that perioperative exposure to Dex-based sedation does not appear to be associated with 1-yr mortality after orthotopic HTX. Rather, this study indicates a reduced 1-yr mortality in patients treated with Dex after HTX.

Postoperative delirium is a common complication in cardiac surgery patients, with an incidence of 9% reported after HTX.[9] The selective alpha-2-agoinst Dex is widely used as a sedative and for prevention of postoperative delirium on the ICU.[3,10] However, referring to the SPICE III trial, Dex-based sedation in patients <65 yr old on the ICU is associated with higher 90-day mortality rates and therefore clinical use has been restricted.[5] A subgroup analysis on the heterogeneity of age-related effect showed that higher mortality was especially associated with Dex treatment in younger non-surgical patients on the ICU.[11,12] While the age of patients undergoing HTX is increasing, a relevant proportion of HTX patients are

Table 1 Baseline patient, surgery, and outcome characteristics of the entire cohort and patients with (Dex) and without (no Dex) dexmedetomidine treatment. Data are presented as mean (standard deviation or range) for continuous variables and numbers (%) for categorial variables. A P-value <0.05 indicates statistical significance. AKI, acute kidney injury; BMI, body mass index; CVVHD, continuous veno-venous haemodialysis; Dex, dexmedetomidine; ECLS, extracorporeal life support; HTX, heart transplantation; IMPACT, risk index for mortality prediction after cardiac transplantation; ns, not significant.

Characteristics mean (SD) or No. (%)	Full dataset (n=169)	No-Dex (n=84)	Dex (n=85)	P-value
Patient characteristics				
Age, yr	55 (22–73)	52 (23–73)	57 (28–71)	0.01
BMI	26 (4)	25 (4)	27 (5)	ns
Sex (male)	47 (28)	24 (29)	23 (27)	ns
Clinical characteristics				
IMPACT score	8.0 (4.1)	7.7 (4.1)	8.3 (4.0)	ns
Arterial hypertension	93 (55)	43 (51)	50 (59)	ns
Diabetes mellitus	31 (18)	13 (16)	18 (21)	ns
Chronic obstructive pulmonary disease	19 (11)	7 (8)	12 (14)	ns
ECLS before HTX	3 (1.8)	1 (1.2)	2 (2.4)	ns
Surgical characteristics				
Duration of surgery, min	390 (98)	396 (103)	384 (92)	ns
Duration of cardiopulmonary bypass, min	237 (60)	242 (61)	231 (59)	ns
Cold ischaemic time, min	145 (41)	148 (43)	142 (39)	ns
Warm ischaemic time, min	63 (14)	64 (14)	62 (15)	ns
Total ischaemic time, min	208 (41)	212 (42)	205 (40)	ns
Outcome				
RBC transfusion	12 (10)	15 (13)	10 (6)	<0.01
1-yr mortality	17 (10)	13 (16)	4 (4.9)	0.03
Severe AKI	91 (54)	48 (57)	43 (51)	ns
CVVHD	65 (39)	35 (42)	30 (35)	ns
Delirium	33 (20)	14 (17)	19 (22)	ns
Re-sternotomy	15 (8.9)	6 (7.1)	9 (11)	ns
Duration of intubation, h	72 (84)	82 (92)	61 (75)	ns
Length of ICU stay, days	19 (21)	20 (26)	19 (13)	ns
Length of in-hospital stay, days	42 (28)	40 (26)	44 (30)	ns

Table 2 Perioperative dexmedetomidine treatment. Time points, dosage, and duration of perioperative dexmedetomidine treatment. Data are presented as mean (standard deviation).Dex, dexmedetomidine; ns, not significant.

	Dex perioperative (*n*=85)	Dex intraoperative (*n*=36)	Dex postoperative (*n*=85)	*P*-value
Dex mean dose, $\mu g\ kg^{-1}\ min^{-1}$	1.1 (0.5)	0.9 (0.3)	1.1 (0.5)	ns
Dex duration, h	29 (20)	31 (24)	29 (20)	ns

still under the age of 65 yr. The mean age in our cohort study was 55 (11) yr. Thus, data from the SPICE III trial might not be fully transferable to HTX patients, especially considering that the highest association between Dex and mortality was seen in non-surgical patients. No underlying explanation for the increased mortality was given in the study. In contrast to results from the SPICE III trial, a systemic review and meta-analysis by Poon and colleagues[4] showed a reduced short-term mortality in patients receiving perioperative Dex-based sedation. Further, several studies indicate that perioperative Dex administration reduces the risk for acute kidney injury after cardiac surgery. As postoperative renal dysfunction has been shown to increase mortality, the occurrence of acute kidney injury after HTX in patients treated with Dex-based sedation should be investigated in further studies. Results from our study show that Dex was not associated with higher 1-yr mortality in this cohort despite patients being under the age of 65 yr. Rather, data from our study seem to suggest a lower risk for 1-yr mortality after HTX in patients with perioperative Dex-based sedation.

Limitations

Because of the study design as a retrospective single-centre study, the results must be evaluated with caution. In order to minimise selection bias, we excluded all patients who needed postoperative treatment with ECLS as these patients are unlikely to be treated with Dex in our hospital. Therefore, a total of 84 patients needed to be excluded from the final analysis. Further, we did not investigate an age-related effect. Lastly, because of the low number of total events of the primary endpoint, adjustment for only three covariables was possible for robust multivariable analysis. Considering these limitations, the safety of Dex-based sedation after HTX should be investigated in a larger cohort study.

Table 3 Cox regression model for influence of perioperative Dexmedetomidine and 1-year mortality. Dex, dexmedetomidine; IMPACT, risk index for mortality prediction after cardiac transplantation; PRBCs, packed red blood cells.

Variables for cox regression	Unstandardised coefficients B	Standard error	Hazard ratio	95% CI	P-value
Perioperative Dex	−1.38	0.66	0.25	0.07–0.93	0.03
IMPACT score	0.13	0.06	1.14	1.01–1.23	0.03
PRBCs	0.03	0.01	1.03	1.00–1.05	0.02

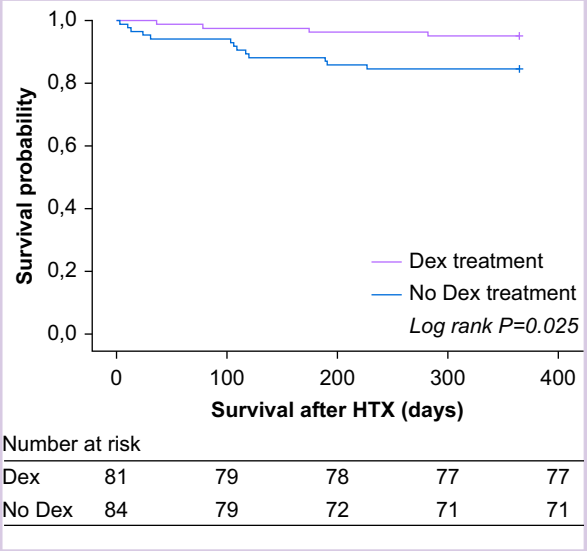

Figure 1. Kaplan–Meier survival curve for dexmedetomidine and 1-yr mortality. The figure shows the Kaplan–Meier survival curve for association of Dex-based sedation with 1-yr mortality after heart transplantation. Dex, dexmedetomidine; HTX, heart transplantation.

Conclusion

Perioperative Dex-based sedation was associated with lower 1-yr mortality in patients undergoing orthotopic HTX. Based on our results, clinical use of Dex as a sedative in HTX patients on the ICU should be considered even in patients <65 yr old.

Authors' contributions

Conceptualization: CT, RM, SR, RH, UB.
Data curation: CT, CLE.
Formal analysis: CT, RM, SR, RH.
Methodology: RM, GLB.
Supervision: GLB, RH, UB.
Writing original draft: CT, RM.
Writing review and editing: SR, AS, HA, AL, GLB, RH, UB.

Declarations of interest

The authors declare that they have no conflicts of interest.

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