The role of dexmedetomidine in the prevention of postoperative delirium in cardiac surgery patients

Význam dexmedetomidínu v prevencii pooperačného delíria u pacientov po kardiochirurgických operačných výkonoch

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Abstract. *Objective*: Post cardiac surgery delirium is a severe complication. Dexmedetomidine is a highly selective shorter-acting intravenous alpha-2-agonist and has a protective effect on specific organs including the heart, brain, kidney and lungs. It was hypothesized that perioperative administration of dexmedetomidine would decrease the incidence of the postoperative delirium in cardiac surgery patients.

Methods: This paper represents a prospective non-randomized clinical observational study. It is a single center study realized in a tertiary level of care facility from April 2013 to February 2014. Two consecutive groups of 250 consecutive patients took part in the study. Group A was the control group and group B was the dexmedetomidine group. In group B, the patients received perioperative dexmedetomidine sedation. The main aim of the measures was to observe the incidence of delirium and to identify any predictors of delirium and to compare the two groups based on the delirium incidence.

Results: The incidence of the delirium was 5.2% in the dexmedetomidine group vs. 20.8% in control group (p=0.001). Predictors of delirium in the dexmedetomidine group were age (p=0.001, 95% CI 1.068-1.271), higher EuroSCORE II value (p=0.035, 95% CI 1.007-1.198), longer CPB time (p=0.018, 95% CI 1.271-13.443), sufentanil dose > 0.15mg (p=0.014, 95% CI 5.394-3.403) and valve combined operations (p=0.036, 95% CI 4.420-1.099). In multivariate analysis only age (p=0.001, 95% CI 1.067-1.303) was a predictor. Comparing the groups together predictors of delirium were age (p=0.001, 95% CI 1.062-1.137), EuroSCORE II value (p=0.001, 95% CI 1.076-1.246), CPB time (p=0.001, 95% CI 1.004-1.015), ACC time (p=0.004, 95% CI 1.003-1.016), sufentanil dose (p=0.010, 95% CI 16.649-61.867), CABG (p=0.015, 95% CI 1.157-3.791).

Conclusion: Perioperative sedation with dexmedetomidine significantly decreases the incidence of postoperative delirium after cardiac surgery and perioperative strategies should continue be developed, in order to further decrease the incidence of the postoperative delirium. Perioperative sedation with dexmedetomidine should be considered in every patient scheduled for cardiac surgery. Tab. 5, Ref. 30, Online full text (Free, PDF) www.cardiology.sk

Key words: dexmedetomidine – prevention – delirium – cardiac surgery

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Abstrakt. *Predmet skúmania:* Delírium po kardiochirurgických operačných výkonoch je závažnou komplikáciou. Dexmedetomidín je vysoko selektívny, krátko účinkujúci, intravenózne aplikovateľný alfa-2-agonista, ktorý pôsobí protektívne na viaceré orgány vrátane srdca, mozgu, obličiek a pľúc. Predpokladá sa, že perioperačná aplikácia dexmedetomidínu by mala znížiť výskyt pooperačného delíria u kardiochirurgických pacientov.
Metodika: Táto práca predstavuje prospektívnu klinickú observačnú štúdiu. Klinická štúdia bola realizovaná v rámci pracoviska so zameraním na poskytovanie terciárnej úrovne zdravotnej starostlivosti v období od apríla 2013 do februára 2014. Štúdia pozostáva z dvoch konsekutívnych súborov, pričom do každého zo súborov bolo zaradených 250 po sebe nasledujúcich pacientov. Prvá skupina predstavuje kontrolnú skupinu a druhá skupinu s dexmedetomidínom. V druhej skupine bol pacientom perioperačne podávaný dexmedetomidín za účelom sedacie. Hlavným cieľom klinickej štúdie bolo sledovať výskyt delíria a identifikovať prediktory delíria, ako aj navzájom porovnať obe skupiny na základe incidencie delíria.
Výsledky: Výskyt pooperačného delíria bol 5,2 % v skupine pacientov s perioperačne podaným dexmedetomidínom v porovnaní s 20,8 % incidenciou v kontrolnej skupine (p = 0,001). Prediktory pooperačného delíria v skupine s dexmedetomidínom predstavovali vek (p = 0,001; 95 % CI 1,068 – 1,271), vyššia hodnota EuroSCORE II (p = 0,035; 95 % CI 1,007 – 1,198), dĺžka trvania mimotelového obehu (p = 0,018; 95 % CI 1,271 – 13,443), dávka sufentanilu > 0,15 mg (p = 0,014; 95 % CI 5,394 – 3,403) a kombinované operačné výkony s intervenciou na úrovni srdcových chlopní (p = 0,036; 95 % CI 4,420 – 1,099). Realizácia multivariate analýzy so vzájomným porovnaním oboch skupín preukázala, že hlavné prediktory pooperačného delíria sú vek (p = 0,001; 95 % CI 1,062 – 1,137), hodnota EuroSCORE II (p = 0,001; 95 % CI 1,076 – 1,246), dĺžka trvania mimotelového obehu (p = 0,001; 95 % CI 1,004 – 1,015), dĺžka naloženia aortálnej svorky (p = 0,004; 95 % CI 1,003 – 1,016), dávka sufentanilu (p = 0,010; 95 % CI 16,649 – 61,867) a CABG (p = 0,015; 95 % CI 1,157 – 3,791).
Zhrnutie: Perioperačná sedacia dexmedetomidínom významne znižuje výskyt pooperačného delíria u pacientov po kardiochirurgických výkonoch. Perioperačná sedacia dexmedetomidínom by sa mala zvažovať u každého pacienta plánovaného na kardiochirurgický operačný výkon. Tab. 5, Lit. 30, Online full text (Free, PDF) www.cardiology.sk
Kľúčové slová: dexmedetomidín – prevencia – pooperačné delírium – kardiochirurgia

Post cardiac surgery delirium is a severe complication which can be developed in any patient during the early postoperative period and is characterized by altered consciousness and global cognitive disturbances. The delirium has been reported to occur in 10% to 60% of surgical patients (1). Moreover in ICU, up to 81% of patients manifest delirium (2).

The alpha-2-receptor agonists (clonidine, dexmedetomidine) currently used in clinical practice have many desirable effects including anxiolysis, inhibition of central sympathetic outflow and reduction of norepinephrine release that improve hemodynamic stability, positively affect myocardial oxygen supply and demand and may provide myocardial protection (3). Dexmedetomidine is a highly selective shorter-acting intravenous alpha-2-agonist with an alpha-2 to alpha-1 selectivity ratio of 1600:1 (4). Different studies have reported that dexmedetomidine has a protective effect on specific organs including the heart, brain, kidney and lungs (5, 6).

However, not so many studies in the literature have explored the impact of dexmedetomidine on the postoperative delirium in cardiac surgery patients.

Thus it was hypothesized that perioperative administration of dexmedetomidine would decrease the incidence of the postoperative delirium in cardiac surgery patients

The aim of this single center prospective non-randomized observational study was to study the effect of the perioperative administration of dexmedetomidine in the prevention of postoperative delirium in cardiac surgery patients.

Methods

In this prospective single center non-randomized observational study the patients were divided into two consecutive groups. The study took place in our institute from April 2013 to February 2014. The first group (group A), which was the control group, included 250 consecutive patients who had various types of cardiac surgery in our institution and were operated on an elective or urgent regime. The second group (group B) included also 250 consecutive patients who received perioperative dexmedetomidine treatment and had various types of cardiac surgery in our institution and were also operated on in an elective or urgent regime. The patients received during sternal wiring a loading dose of 0.4μg/kg, followed by a maintenance drip of 0.25μg/kg/h for a maximum dose of 200μg. Patients that were operated on in an emergency regime were excluded from the study. Of the patients who participated in both groups, medical history and preoperative characteristics (concomitant diseases or risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcoholism, previous psychiatric disease), perioperative details

(type of operation, duration of cardiopulmonary bypass and aortic cross-clamp, doses of opiates and benzodiazepines administered during the operation) and post-operative details (duration of mechanical ventilation > 24 hours, ICU and hospital stay) were recorded.

Also the EuroSCORE II value was calculated for all patients in both groups and according to it they were categorized into three groups as high, moderate and low risk (low risk <1.6%, moderate risk 1.6%-6.7%, high risk >6.7%).

Cardiac surgery, the anesthetic regimen and the post-operative management were standardized.

Ethics

Ethical approval for this study was provided by the Ethical Committee of the Eastern Slovak Institute for Cardiovascular Diseases, Kosice, Slovakia (Chairman Juhas S. MD, PhD) on the 30/9/2013.

All the study participants provided a written informed consent.

Anesthetic technique

All patients in both groups received premedication of 10mg oxazepam the evening before surgery and 7.5mg of midazolam 1 to 2 h before surgery. Anesthesia was induced by 2.5-5mg midazolam, 2-2.5mg/kg propofol, sufentanil 0.01-0.025mg and sevoflurane 1-2%. Tracheal intubation was facilitated by 0.6-1mg/kg tracrium. Anesthesia was maintained with sufentanil infusion 0.0005 mg/kg/h and sevoflurane 1-2%, while neuromuscular blockade was maintained with the administration of tracrium 50mg every 40 minutes. No propofol was administrated during anesthesia maintenance.

Surgery-conduct of cardiopulmonary bypass

All surgery procedures were performed through median sternotomy. No-touch aorta technique was used in off-pump surgery. Nasopharyngeal temperature was maintained above 35°C and systolic blood pressure was kept at 80mmHg or greater throughout the procedure.

For patients undergoing on-pump surgery anticoagulation was achieved with heparin to maintain an activated clotting time above 480s and the cardiopulmonary bypass circuit was primed with 1l of Ringer's Lactate and 250ml of 20% mannitol. Mild hypothermia of 34-35°C was induced during cardiopulmonary bypass, the pump flow rate was 2.4-2.8 l/min/m^2 and the mean perfusion pressures were between 70-75mmHg. Hematocrit was kept between 25-35%. Myocardial protection was achieved with intermittent blood-enriched cold cardioplegic solution (3°-6°C of St. Thomas cardioplegic solution) using a blood to crystalloid ratio of 5:1. Fractional concentration of inspired oxygen was adjusted to keep arterial oxygen tension between 150-250mmHg, and gas flow was adjusted to maintain arterial carbon dioxide tension between 35-40mmHg without temperature correction (α-stat).

Postoperative management

After surgery, all the patients were admitted to the cardio-surgical ICU, where a standard protocol was implemented for sedation, analgesia and management of mechanical ventilation. Patients were extubated according to the following criteria: responsive and cooperative, pO_2 of 10-11kPa and oxygenation index of pO_2/FiO_2 > 300. In the ICU patients were sedated with propofol until extubation. Analgesia was provided with intravenous morphine infusion at 2mg/h, algifen (metamizole, pitofenone, fenpiverinium) 2.5g every 8 hours and intravenous tramadol 100mg every 8 hours.

Delirium assessment

Delirium was assessed with the CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) every 12 hr postoperatively. The CAM-ICU allows the monitoring of delirium in both ventilated and extubated patients. It is based on the Diagnostic and Statistical Manual of Mental Disorders criteria and includes a 4-step algorithm. The patient is determined to be delirious (CAM-positive) if he or she manifests standard features for delirium.

All cardiovascular ICU nurses were educated and well trained in the application of the CAM-ICU in both ventilated and non-ventilated patients.

The level of sedation (level of arousal) was assessed by means of the The Richmond Agitation Sedation Scale (RASS).

Statistical analysis

Data are given as mean value +/- standard deviation (SD). Categorical variables are presented as numbers of patients (percentage). A univariate analysis was performed to identify perioperative risk factors in both groups associated with delirium using Chi-square analyses or Fisher's Exact Test. Different cut-off points for continuous variables were examined to determine the best association with delirium. Odds ratios (OR) were calculated to indicate the effect size of perioperative risk factors on delirium. Variables associated with outcome with a p value <0.05 in the univariate analyses and variables considered clinically significant were entered into a multiple logistic regression model for delirium in order to identify independent risk factors. This was performed by using stepwise logistic regression technique. Finally, both groups A and B were between them statistically matched, analyzed and compared.

For statistical analysis the SPSS software version 22 (SPSS Inc., Chicago, IL, USA) was used.

Results

Two groups of 250 eligible patients in each were included in the study. 52 (20.8%) developed delirium from group A and 13 (5.2%) patients from group B with the incidence

of delirium between the groups being statistically significant (p=0.001). The patients developed a hyperactive and mixed type of delirium with hyperactive and hypoactive activity.

The preoperative, perioperative and postoperative clinical patients´ characteristics of the two groups and the comparison of groups are shown in **Table 1**.

Patients with postoperative delirium in both groups had a longer stay in the ICU (p<0.0001, p=0.015 respectively) and patients in group A longer total duration of hospitalization compared with group B (p<0.0001, p=0.125 respectively), however the ICU stay is not a predictor of postoperative delirium (p=0.534) in the control group.

Univariate analysis of the variables of group A confirmed that older age (p<0.0001), a higher EuroSCORE II value (p<0.0001), a longer CPB time (p<0.0001), a longer ACC time (p<0.0001), and the sufentanil dose (p=0.010) were strongly independently associated with postoperative delirium.

In multivariate analysis of the variables of group A age (p<0.001), a EuroSCORE II value (p<0.001), the CPB and ACC time (p<0.05), the sufentanil dose (p<0.001), benzodiazepine administration (p<0.05) and the CABG type of operation (p<0.001) are all predictors of postoperative delirium development.

Univariate analysis of the variables of group B confirmed that older age (p=0.001), the higher EuroSCORE II value (p=0.035) were strongly associated with the development of delirium. Concerning CPB time >120min, it was also shown to be a predictor for developing postoperative delirium (p=0.018). ACC time > 60 min was found to be a weak predictor for developing postoperative delirium (p=0.085). Moreover a sufentanil dose >0.15mg was also found to be a predictor for developing postoperative delirium (p=0.014).

In group A in patients who had CPB time more than 120 min had a 15 times higher risk for developing postoperative delirium. Also the longer the ACC time the higher the risk for developing postoperative delirium. Finally, the higher the sufentanil dose (the patients were running a fixed dose per Kg per minute), the higher the risk for developing postoperative delirium. From this analysis we see that certain variables such as CPB and ACC time and sufentanil dose are

Table 1 The preoperative, perioperative and postoperative clinical patients´characteristics: comparison of control group and dexmedetomidine group

Variable	Control group	Dexmedetomidine group	*P*
	Total (*n*=250)	Total (*n*=250)	value
Age, (years) mean+/-SD	65.2+/-10.3	64.9+/-10.5	0.701
Men	171 (68.4%)	166 (66.4%)	0.702
Women	79 (31.6%)	84 (33.6%)	
Diabetes mellitus	77 (30.8%)	84 (33.6%)	0.502
Arterial hypertension	229 (91.6%)	225 (90.0%)	0.536
Hypercholesterolemia	187 (74.8%)	196 (78.4%)	0.341
Smoking	88 (35.2%)	96 (38.4%)	0.458
Alcoholism	26 (10.2%)	7 (2.8%)	0.001
Psychiatric disorder in the medical history	22 (8.8%)	15 (6.0%)	0.232
EuroSCORE II, (%) mean+/-SD	2.63+/-2.65	3.18+/-3.82	0.152
Operation type			
CABG	104 (41.6%)	112 (45.6%)	0.066
AVR	50 (20.0%)	33 (13.2%)	0.064
MVR	20 (8.0%)	13 (5.2%)	0.450
CABG + AVR	27 (10.8%)	25 (10.0%)	0.363
OPCAB	32 (12.8%)	25 (10.0%)	0.395
Other (ASD, Myxoma, Bentall)	2 (0.8%)	14 (5.6%)	0.001
ACC (min), mean+/- SD	55.11+/-38.61	56.47+/-39.65	0.001
CPB (min), mean+/-SD	72.90+/-45.46	76.27+/-47.85	0.001
Sufentanil (mg), mean+/-SD	0.15+/-0.03	0.15+/-0.04	0.001
Benzodiazepines (mg), mean+/-SD	4.73+/-2.86	3.53+/-3.42	0.017
Mechanical ventilation (hours), mean+/-SD	3.70+/-2.39	4.78+/-6.56	0.008
ICU stay (days), mean+/-SD	4.62+/-3.47	4.33+/-3.24	0.337
Hospitalization (days), mean+/-SD	10.84+/-6.85	9.71+/-4.79	0.034

N – number, SD – standard deviation, CABG – coronary artery bypass graft surgery, AVR – aortic valve replacement, MVR – mitral valve replacement, OPCAB – off-pump coronary artery bypass, ASD – atrial septal defect, ACC – aortic cross-clamping, min – minute, CPB –cardio-pulmonary bypass, mg – milligram, ICU – intensive care unit

all linked to a common parameter: time, so as a conclusion, the longer the operation lasts, the higher the risk for developing postoperative delirium.

In group B, the administration of dexmedetomidine in the univariate analysis did not completely eliminate the parameter of time in the development of postoperative delirium.

Concerning the benzodiazepine administration, it was shown in group A to be a weak predictor for developing postoperative delirium (p=0.055) in univariate analysis and a strong predictor in multivariate analysis (p<0.050) where in group B it was shown not to be a predictor for the development of postoperative delirium (p=0.334).

Concerning the type of surgery in group A, CABG was shown to be associated with the incidence of postoperative delirium (p=0.010), where in group B valve combined operation was found to be a predictor of delirium (p=0.036). In multivariate analysis of the variables in group A, age (p<0.001), EuroSCORE II value (p<0.001), CPB and ACC time (p<0.05), sufentanil dose (p<0.001), benzodiazepine administration (p<0.05) and the CABG type of operation (p<0.001) are all predictors of postoperative delirium development. In group B in multivariate analysis only age was shown to be a predictor of postoperative delirium development (p=0.001).

Table 2 shows the univariate analysis of the variables in group A, **Table 3** shows the univariate analysis of the variables in group B and **Table 4** shows the multivariate analysis of both groups.

The incidence of delirium according to each variable between the two groups is shown in **Table 1**.

After comparison of the two groups older age (p=0.001), higher EuroSCORE II (p=0.001), CABG type of operation (p=0.015) were all confirmed to be associated with an increased risk for the development of postoperative delirium. Perioperative predictors connected with the operative time, such as CPB time (p=0.001), ACC time (p=0.004), sufentanil dose >0.15mg (p=0.010) were also associated with an increased risk for the development of postoperative delirium. Finally, patients who suffered from delirium had prolonged ICU stay (p=0.001) and hospitalization time (p=0.001).

The statistical comparison analysis of the variables of both groups based on the incidence of the postoperative delirium is shown in **Table 5**.

The hospital mortality was 1.6% and 1.2% in group A and group B respectively.

Table 2 Univariate analysis of the variables in control group

S. Nº.	Variable	Nº.	Delirium Nº. (%)	No delirium Nº. (%)	*Sig. P* value	*Exp (B) OR*	*95% C.I. For Exp (B)OR*	
							Lower	*Upper*
1.	Age, (years)	250	52 (20.8)	198 (79.2)	<0.0001	1.090	1.048	1.133
2.	Gender	250	52	198	0.616	0.842	0.431	1.646
3.	EuroSCORE II	250	52 (20.8)	198 (79.2)	<0.0001	1.348	1.187	1.153
4.	D. Mellitus	77	21 (27.3)	56 (72.7)	0.991	1.706	0.904	3.217
5.	Hypertension	229	49 (21.4)	180 (78.6)	0.441	1.642	0.465	5.805
6.	Hypercholest.	187	36 (19.3)	151 (80.7)	0.309	0.705	0.359	1.383
7.	Smoking	88	13 (14.4)	75 (85.6)	0.082	0.542	0.272	1.082
8.	Alcoholism	26	5 (19.2)	21 (80.8)	0.827	0.892	0.319	2.490
9.	Psych. Disease	22	2 (9.1)	20 (90.9)	0.171	0.354	0.080	1.566
10.	ACC time (min)	250			0.003	1.010	1.003	1.017
	>60	149	36 (24.2)	113 (75.8)	<0.001			
11.	CPB time, (min)							
	>120	18	10 (55.6)	8 (44.4)	<0.0001	15.188	3.749	61.626
12.	Sufentanil d.(mg)	250	52 (20.8)	198 (79.2)	<0.0101	12.419	16.649	92.644
13.	Benzo. d. (mg)	250	52 (20.8)	198 (79.2)	0.055	1.120	0.998	1.257
14.	M. Vent. >24 (h)	0	0	0	n/a	n/a	n/a	n/a
15.	ICU stay, (days)	250	52 (20.8)	198 (79.2)	<0.0001	1.256	1.137	1.387
16.	Hosp.stay, (days)	250	52 (20.8)	198 (79.2)	<0.0001	1.112	1.056	1.172
17.	Operation type	250	52 (20.8)	198 (79.2)				
	CABG	104	20 (19.2)	84 (80.8)	0.010	2.427	1.238	4.760
18.	Valve comb., OS	114	26 (29.6)	88 (70.4)	0.460	1.269	0.674	2.390

S.– subject, Nº. – number, sig. – significant, Exp(B) – coefficient, OR – odds ratio, C.I. – confidence interval, D. – diabetes, Hypercholest. – hypercholesterolemia, Psych. – psychiatric, ACC – aortic cross-clamping, min – minute, CPB – cardio-pulmonary bypass, d. – dose, mg – milligram, Benzo. – benzodiazepine, M. Vent. – mechanical ventilation, h – hours, n/a – not applicable, ICU – intensive care unit, Hosp. – hospitalization, CABG – coronary artery bypass graft surgery, comb. – combined, OS – other surgery

Table 3 Univariate analysis of the variables in dexmedetomidine group

S. Nº.	Variable	Nº.	Delirium Nº. (%)	No delirium Nº. (%)	*Sig. P* value	*Exp(B) OR*	*95% C.I. For Exp (B)OR*	
							Lower	*Upper*
1.	Age, (years)	250	13 (5.2)	237 (94.8)	0.001	1.166	1.068	1.271
2.	Gender	250	13	237	0.840	0.883	0.264	2.957
3.	EuroSCORE II	250	13 (5.2)	237 (94.8)	0.035	1.098	1.007	1.198
4.	D. Mellitus	84	6 (7.1)	78 (92.9)	0.336	1.736	0.564	5.341
5.	Hypertension	225	13 (5.8)	212 (94.2)	0.998	10.093	0.000	
6.	Hypercholest.	196	11 (5.6)	185 (94.4)	0.574	1.554	0.334	7.234
7.	Smoking	96	4 (4.2)	92 (95.8)	0.555	0.696	0.208	2.325
8.	Alcoholism	7	1 (14.3)	6 (85.7)	0.300	3.194	0.356	28.689
9.	Psych. disease	15	1 (6.7)	14 (93.3)	0.796	3.321	0.160	10.902
10.	ACC time, (min)	250	13 (5.2)	237 (94.8)	0.127	1.009	0.997	1.020
11.	CPB time, (min)	250	13 (5.2)	237 (94.8)	0.121	1.008	0.998	1.017
12.	Sufentanil d.(mg) >0.15	74	6 (8.1)	68 (91.9)	0.014	5.394	3.403	34.490
13.	Benzo. d. (mg)	250	13 (5.2)	237 (94.8)	0.334	1.071	0.931	1.232
14.	M. vent. (h)	250	13 (5.2)	237 (94.8)	0.999	1.000	0.918	1.089
15.	ICU stay	250	13 (5.2)	237 (94.8)	0.015	1.142	1.026	1.272
16.	Hosp.stay, (days)	250	13 (5.2)	237 (94.8)	0.125	1.065	0.982	1.155
17.	Operation type							
	OPCAB	25	1 (4.0)	24 (96.0)	0.773	0.736	0.092	5.911
	CABG	112	4 (3.6)	108 (96.4)	0.746	1.221	0.365	4.084
18.	Valve comb., OS	113	8 (7.1)	105 (92.9)	0.036	4.420	1.099	17.784

S. – subject, Nº. – number, sig. – significant, Exp(B) – coefficient, OR – odds ratio, C.I. – confidence interval, D. – diabetes, Hypercholest. – hypercholesterolemia, Psych. – psychiatric, ACC – aortic cross-clamping, min – minute, CPB – cardio-pulmonary bypass, d. – dose, mg – milligram, Benzo. – benzodiazepine, M. vent. – mechanical ventilation, h – hours, ICU – intensive care unit, Hosp. – hospitalization, OPCAB – off-pump coronary artery bypass, CABG – coronary artery bypass graft surgery, comb. – combined, OS – other surgery

Table 4 Multivariate analysis of the variables of both groups

Variable	Control group OR (95% C.I.)	*P* value	Dexmedetomidine group OR (95% C.I.)	*P* value
Age	1.106 (1.061-1.155)	<0.050	1.179 (1.067-1.303)	0.001
EuroSCORE II	1.331 (1.171-1.514)	<0.050		
CPB time	1.009 (1.002-1.016)	<0.050		
ACC time	1.010 (1.002-1.019)	<0.050		
Sufentanil dose	5.657 (2.159-14.821)	<0.001		
Benzodiaz. admin.	2.056 (1.036-4.081)	<0.050		
CABG	6.142 (2.248-16.782)	<0.001		

OR – odds ratio, C.I. – confidence interval, CPB – cardio-pulmonary bypass, ACC – aortic cross-clamping, Benzodiaz. – benzodiazepine, admin. – administration, CABG – coronary artery bypass graft surgery

Discussion

This single centre prospective non-randomized observational study found that sedation with dexmedetomidine was associated with a significantly reduced incidence of post-operative delirium in patients undergoing cardiac surgery. The incidence of delirium in the control group was 20.8%, where as in contrast the incidence of delirium for patients receiving dexmedetomidine was 5.2%. Similarly Maldonado et al. (7) in a randomized trial also found that the incidence of delirium in patients receiving dexmedetomidine was 3%, significantly lower than patients receiving propofol or midazolam sedation.

Moreover the DEXCOM (8) randomized trial compared the prevalence of delirium with dexmedetomidine versus morphine based sedation in patients undergoing cardiac surgery. It illustrated a trend toward a lower rate of delirium in the dexmedetomidine group, with a significantly shorter duration of delirium (p=0.037).

Table 5 The statistical comparison analysis of the variables in both groups based on the incidence of the postoperative delirium

S. Nº.	Variable	Nº.	Delirium Nº. (%)		No delirium Nº. (%)	*Sig. P* value	*Exp (B) OR*	*95% C.I. for Exp(B) OR*	
			Control group	*Dexmede. group*				*Lower*	*Upper*
	Incidence		20.8%	5.2%		0.001	0.209	0.110	0.394
1	Age, (years)					0.001	1.099	1.062	1.137
2	Gender					0.543	0.838	0.473	1.482
3	EuroSCORE II					0.001	1.158	1.076	1.246
4	D. Mellitus					0.091	1.585	0.930	2.704
5	Hypertension					0.179	2.279	0.686	7.570
6	Hypercholest.					0.702	0.838	0.558	1.564
7	Smoking					0.071	0.575	0.316	1.049
8	Alcoholism					0.920	1.050	0.407	2.706
9	Psych. disease					0.359	0.568	0.169	1.905
10	**Operation type**								
	CABG					0.015	2.095	1.157	3.791
	OPCAB					0.742	0.866	0.366	2.045
	AVR					0.597	1.164	0.662	2.049
	MVR					0.139	1.688	0.844	3.374
	OS					0.141	2.770	0.713	10.758
11	CPB time					0.001	1.009	1.004	1.015
12	ACC time					0.004	1.009	1.003	1.016
13	Sufentanil d. (mg) >0.15					0.010	24.111	16.649	61.867
14	Benzodiaz.					0.234	0.944	0.860	1.038
15	M. vent.					0.302	1.023	0.980	1.067
16	ICU stay					0.001	1.206	1.123	1.295
17	Hosp. stay					0.001	1.098	1.054	1.144

S. – subject, Nº. – number, sig. – significant, Exp(B) – coefficient, OR – odds ratio, C.I. – confidence interval, dexmede. – dexmedetomidine, D. – diabetes, Hypercholest. – hypercholesterolemia, Psych. – psychiatric, CABG – coronary artery bypass graft surgery, OPCAB – off-pump coronary artery bypass, AVR – aortic valve replacement, MVR – mitral valve replacement, OS – other surgery, CPB – cardio-pulmonary bypass, ACC – aortic cross-clamping, d. – dose, mg – milligram, Benzodiaz. – benzodiazepine, M. vent. – mechanical ventilation, ICU – intensive care unit, Hosp. – hospitalization

Dexmedetomidine was shown in two European randomized double-blind double-dummy trials (PRODEX and MIDEX) to be non-inferior to propofol and midazolam in maintaining target sedation levels in mechanically ventilated intensive care unit (ICU) patients. Additionally, dexmedetomidine shortened the time to extubation versus both standard sedatives, suggesting that it may reduce ICU resource needs and thus lower ICU costs (9).

Finally a meta-analysis by Lin YY (10) also confirmed that sedation with dexmedetomidine reduced the incidence of delirium following cardiac surgery (p=0.0004).

In the dexmedetomidine group older age, the higher EuroSCORE II, longer CPB time and increased sufentanil dose value were shown to be strongly associated with the development of delirium. From the results it was shown that the administration of dexmedetomidine did not eliminate the predictor effect of the CPB time and the sufentanil dose in the development of postoperative delirium.

After comparison of the two groups older age, a higher EuroSCORE II, and CABG type of operation were all confirmed to be associated with an increased risk for the development of postoperative delirium. Perioperative predictors connected with the operative time, such as CPB time, ACC time, sufentanil dose >0.15mg were also associated with an increased risk for the development of postoperative delirium.

Age has consistently been reported as a predictor of postoperative delirium (11). Moreover, concerning EuroSCORE value Osse RJ et al (12) found that EuroSCORE value greater than 6 was associated with the incidence of the postoperative delirium.

Another two intraoperative predictors found in our study to be associated with postoperative delirium are longer CPB and ACC times. Other reports published in the literature have similar results. Andrejaitiene J et al (13) found that ACC time >68 min is associated with the development of delirium. Similar results are reported by other authors reporting that increased CPB times are associated with the development of postoperative delirium (14). It has been hypothesized that cerebral atherosclerosis combined with

postsurgical inflammatory changes may inhibit cerebral blood flow which may be exacerbated by the non-pulsatility of CPB (15). Longer duration of surgery is correlated with longer CPB and Brown WR et al (16) showed that increased duration of CPB was associated with increased gaseous embolic load to the brain. Also longer surgical duration may also mean a more complex procedure, perhaps requiring more heart and major vascular manipulation, with resultant embolic phenomena.

Moreover, increased ventilation time was also associated with the postoperative delirium (17). Other authors showed that the duration of ventilation (prolonged ventilation >24 hours (18)) is as independent predictor of postoperative delirium.

Furthermore, it was shown that the higher the sufentanil dose (the patients in our study were running a fixed dose per Kg per minute), the higher the risk for developing postoperative delirium. The sufentanil dose is linked with time so the longer the duration of the operation, the higher the sufentanil dose, the higher risk for developing postoperative delirium. This association was investigated also by other authors. Burkart CS et al (19) showed that an increasing dose of fentanyl administered intraoperatively appeared to be a risk factor for postoperative delirium.

Gunaydin B et al (20) found a higher rate of delirium in patients after high dose fentanyl anesthesia compared with barbiturate anesthesia without the use of fentanyl. Comparing remifentanil with fentanyl in cardiac surgery Cheng DC et al (21) found a significantly lower rate of confusion in the remifentanil group. Alternative use of remifentanil should be considered in strategies focusing on the prevention of delirium.

Concerning the benzodiazepine dose, it was also shown in the control group to be a weak predictor for developing postoperative delirium where in the dexmedetomidine group it was not a predictor of postoperative delirium. Pandharipande P et al (22) also showed that exposure to benzodiazepines is one of the strongest modifiable risk factors for postoperative delirium development. In our study the patients developed a hyperactive and mixed type of delirium. McPherson JA et al (23) showed that patients who received benzodiazepines and are restrained after heart surgery had hypoactive type of delirium. Avoiding chemicals restraints via use of benzodiazepines or the use of physical restraining via use of benzodiazepines or the use of physical restraint devices and as much early mobilization as possible could be an effective preventive strategy in order to decrease the development of postoperative delirium. In our department a patient with an uncomplicated postoperative course is usually mobilized on postoperative day 4, so there is room for improvement in this issue.

Concerning the type of operation in our study only CABG in the control group and CABG combined with valve operation in the dexmedetomidine group were associated with the development of postoperative delirium. Other authors showed also a higher incidence of delirium in patients undergoing valve replacement and combined surgery with valve replacement and CABG compared with patients undergoing isolated coronary artery bypass graft surgery (24). The reason for this according to the authors may be the embolic load of air which is trapped within the cardiac chambers, or particulate matter during the valve replacement surgery is higher than in CABG patients. Concerning our study, the relatively small sample size of valve replacement patients compared with the CABG patients sample could be responsible for the fact that in our patients population CABG surgery alone or combined with valve surgery and not valve surgery is associated with the development of postoperative delirium.

In our study the time frame for early post cardiac surgery delirium is defined as 2-6 days after the operation, since delirium diagnosed on the first or after the sixth day following cardiac surgery might not be directly connected to the surgery (25).

At least two sets of theories can be used to explain the fact that the patients in the dexmedetomidine group experienced a lower incidence of postoperative delirium. The first suggests that dexmedetomidine has intrinsic delirium-sparing effects. First, dexmedetomidine has high and specific receptor selectivity. Studies have suggested that the likelihood of delirium is increased with the number of neurotransmitter pathways disrupted (4, 26). The second characteristic is its effect in presynaptic noradrenergic transmission. Changes in the system have been described as potential causative factors in delirium (27). Third, dexmedetomidine produces sedation without respiratory depression. Hypoxia and anoxia in the CNS lead to delirium (28). Finally, dexmedetomidine lacks clinical anticholinergic effects, patients have lower opioid requirements and promotes a more physiologic sleep-wake cycle in the ICU setting (29, 30).

The second theory suggests that the reason patients had significantly less delirium in the dexmedetomidine group was not because of its use per se, but because those patients were not exposed to other agents that may have a much greater delirium potential.

In the literature there are not many studies which examine the role of dexmedetomidine sedation in the prevention of the postoperative delirium and especially in the group of patients after cardiac surgery which we examined, and this may be considered one of the strengths of this study. Secondly, the patients included in this study represent a real world selection group and finally, the operative techniques, the postoperative management and medications are standardized across the groups to minimize the impact of their use.

It was observed that after the two group comparison age, EuroSCORE II value, CPB and ACC time, higher sufentanil

dose and CABG type of surgery emerged as predictors of postoperative delirium. Even though the administration of dexmedetomidine significantly decreased the incidence of the postoperative delirium all the above predictors increase the risk for the development of postoperative delirium. Intra and perioperative strategies should be developed, despite the positive effect of the dexmedetomidine sedation in order to further decrease the incidence of postoperative delirium in cardiac surgery patients.

The study has some limitations. Firstly this is a prospective non-randomized observational study. A more powerful randomized, placebo-controlled, double blind trial should be performed in order to confirm the results of this study. Secondly, we did not perform baseline psychiatric and cognitive screening tests as preoperative mental disorders are strong predictors of postoperative delirium. Any psychiatric disorders that were examined in our study were obtained from the medical history of the patient and their incidence could be underestimated. Thirdly, the CAM-ICU assessment was performed in the cardiovascular ICU and was not extended to the cardiac surgical floor. As a result, our findings can only be applied to early postoperative delirium. Moreover, we did not examine the association of the various perioperative medications (e.g. inotropic support) with the development of postoperative delirium. Lastly, our study mainly focused on preoperative and perioperative predictors and did not include postoperative variables.

Conclusion

Dexmedetomidine sedation significantly decreases the incidence of postoperative delirium after cardiac surgery. Even, after dexmedetomidine sedation, risk factors such as age, EuroSCORE II value, CPB and ACC time, sufentanil dose and CABG operation type may increase to a lesser degree the risk of postoperative delirium, intra and perioperative strategies should be developed in order to further decrease the incidence of the postoperative delirium in cardiac surgery patients. Dexmedetomidine sedation should be considered in every patient scheduled for cardiac surgery.

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