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Communication

Comparison of the Use of Desflurane vs. Propofol in Aortic Valve Replacement Surgery: Differences in Nephroprotection

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Abstract: *Introduction:* The effect of halogenated drugs as cardioprotectors in cardiac surgery has been evaluated in several studies. However, the possibility that there is a protective role at renal level, triggered by their use, is currently under study. Aortic valve replacement and coronary revascularization are the most frequent surgeries in cardiac surgery. Our research evaluates the effect of desflurane compared to propofol in aortic valve replacement surgery at renal level; including its administration during extracorporeal circulation. *Method:* Quasi-experimental prospective study performed on 60 patients, divided into 2 groups according to the drug used in intraoperative aortic valve replacement surgery. In group 1 propofol was used as a hypnotic during surgery, in group 2 desflurane was used. Differences in kidney damage measured through the urinary NGAL marker were evaluated. Other markers of renal function and myocardial damage and the need for inotropic support during the first 48 hours were also measured. *Results:* There were significant variations in the values of urinary NGAL and creatinine regarding to basal values in the propofol group, but not in the desflurane group, in which there were no differences in the hemodynamic parameters and myocardial damage. *Conclusion*: the use of desflurane during aortic valve replacement surgery produced better renal preservation than propofol.

Keywords: desflurane; cardiac surgery; halogenated; kidney; heart; preconditioning

1. Introduction

The use of halogenated agents in the intraoperative period of cardiac surgery has shown multiple benefits, mainly related to the effect at the cardiac level [1–3].

The effect of desflurane on the heart facilitates its preservation, thanks to pre- and post-conditioning, in situations of induced ischemia (during extracorporeal circulation) or in patients with high risk of coronary events due to ischemic heart disease in the perioperative period of cardiac surgery [4]. Unlike the intravenous agents (propofol), the enzymatic pathways are amplified in relation to time and concentration of the anesthetic gas used; reason why the maintenance of its administration during the extracorporeal circulation should play a fundamental role in its effect, because at this time, the myocardium increases its risk of suffering damage, in relation to its disease and possible imbalances between oxygen supply and consumption [2,5–8].

The clinical effect of using halogenated agents in the perioperative period of cardiac surgery is related to the decreased low cardiac output syndrome and myocardial damage markers [9,10].

The role of these drugs in connection with perioperative organ protection has been the subject of study in recent years. The kidney has been the fundamental objective of numerous studies due to its relationship with the mortality of patients in the postoperative period of cardiac surgery. Different investigations correlate the improvement of renal

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function with the use of halogenated, thanks to a double role. Firstly, a better cardiac output associated with its better preservation thanks to the myocardial conditioning action and secondly, a possible effect of halogenated at kidney level associated with mechanisms similar to myocardial in this organ [6,10].

From the range of drugs used in cardiac surgery, sevoflurane is the halogenated most widely chosen in several investigations. However, different studies have proposed the benefit of desflurane in this type of interventions, although its administration during cardiopulmonary bypass has been evaluated by a small number of studies, and with the main objective of seeing its action at the cardiac level [11].

Our study evaluates the renal effects of the use of desflurane compared to propofol in patients undergoing aortic valve replacement, through the measurement of urinary NGAL, a specific and high sensitivity biochemical parameter of kidney damage, and with determinations of creatinine and diuresis (parameters related to renal dysfunction).

In addition, the degree of cardiac preservation between the 2 study groups will be evaluated with the purpose of knowing the biochemical (Troponin I, NTProBNP) and clinical repercussion of the use of desflurane during the intraoperative compared with propofol.

2. Materials and Methods

Prospective observational study performed on Virgen de la Victoria hospital. The study was approved by the Malaga Norte Ethics Committee and subsequently the informed consent was signed by all the patients after their explanation. The study was carried out in accordance with the regulation of the Declaration of Helsinki. The recruited patients were going to undergo aortic valve replacement surgery and met inclusion/exclusion criteria:

Inclusion criteria: 1. Elective aortic valve replacement surgery. 2. EUROSCORE (European scale of risk, useful in the perioperative period of patients undergoing cardiac surgery, validated at medical and scientific level) less than 8 (moderate cardiological risk in the perioperative period). 3. Degree of anesthetic risk according to the American Society of Anesthesia (ASA) less than or equal to 4 (patient with moderate-high anesthetic risk).

Exclusion criteria: 1. Clinical history of adverse reaction to different anesthetic drugs. 2. Severe disease of any organ (lung, liver, kidney) diagnosed preoperatively. 3. Combined surgery (e.g. aortic valve and carotid surgery). 4. Patients with hemodynamic instability. 5. Heart failure or need to use inotropic or vasoactive drugs prior to intervention. 6. Treatment with oral antidiabetics not suspended for at least 48 hours before. 7. Treatment with euphylline/theophylline prior to intervention.

The administration of the drug was assigned by the anesthesiologist in charge before the start of the study.

Group 1: intraoperative propofol.

Group 2: Intraoperative desflurane.

The hemodynamic management of low cardiac output syndrome was performed according to the consensus and recommendation document of the spanish society of anesthesiology and resuscitation. Management of diuresis less than 1 ml/min was done optimizing hemodynamics according to protocol (start of treatment of the LCOS and MAP in variations not greater than 15 with respect to basal level), if after 1 hour since treatment begins diuresis is less than 1ml/kg/h should proceed to the administration of 500 ml of crystalloid (Plasmalyte) in 30 minutes, repeating again if the result is not satisfactory, as long as systolic volume variation (SVV) is less than 10% and if there is no response, administer 10 mg of furosemide every 30 minutes until a favorable response is achieved. If the urine output is greater than 1 ml/kg/h no diuretic drug should be administered.

All patients will be monitored with a 5-lead electrocardiogram. In all of them, a continuous record will be kept of lead II and V, of invasive blood pressure through the radial artery and of cardiac output through the Mostcare monitor. Pulse oximetry, capnography

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and blood pressure monitoring will also be performed through bispectral index (BIS) hypnosis (BIS XP®; Aspect Medical Systems, Newton, MA) provided that the patient remains sedated and connected to mechanical ventilation with an adequate concentration to maintain the values of hypnosis in the sedation ranges described (60-70).

In all the recruited patients, the epidemiological data of age, sex and EUROSCORE (risk of perioperative mortality for patients undergoing surgery Cardiac) will be collected. Intraoperative: ECC time, ischemia time.

Biochemical analysis: troponin I, CK, CKMMB, creatinine, lactate, NT-ProBNP and urinary N-Gal. These determinations will be collected from the time of diagnosis, previous to the intervention and during the following 48 hours, every 24 hours. N-GAL will be collected at baseline and at 2 hours of arrival to recovery.

Hemodynamic determinations: heart rate, mean arterial pressure, right ventricular end-diastolic pressure, SatVO2, diagnosis of low cardiac output syndrome CI<2 l/min/m² or SatVO2<65% after hemodynamic optimization or need to use inotropic drugs. These parameters will be calculated every 12 hours after entering the operating room, for the next 48 hours.

Renal function parameters: diuresis, creatinine, need for furosemide or renal replacement therapy, stage according to AKI scale (Acute Kidney Injury); every 6 hours until 48 hours after admission.

Sample size justification

URINARY N-GAL determined 2 hours after surgery has been shown to be an effective and early marker of kidney failure according to Prabhu et al. A sample size was calculated in order to distinguish a difference of 150 ng/ml in urine before and after administration of the drug. 27 patients were necessary to achieve a beta statistical power of 80% and α=0.05. 10% losses are assumed so 30 patients per group were necessary (calculations performed with statistical program Prism 9 GraphPad).

3. Results

Normal distribution was studied using Shapiro-Wilk normality test and sample variance distribution using the Levenne test. Results with normal or non-normal distribution but with n=30 per group were analyzed using the t-test for normal distributions and homogeneous variances. Non-normal distributions were analyzed using Mann–Whitney–Wilcoxon test. Binary variables were analyzed with Two-Proportions Z-Test. There were no significant differences between groups in the epidemiological and intraoperative variables collected. Table 1.

Table 1. Epidemiological variables.

	Propofol	Desflurane	p
Ischemia time	45	43	0.84
ECC time	82	83	0.95
Age (years)	68	65	0.33
Gender (M/F)	0.57	0.47	0.44

ECC: extracorporeal circulation.

There were no differences in the hemodynamic parameters monitored during the study. Table 2. In the kidneys, there were no significant differences between groups, biochemical parameters and stage of kidney function. Table 3.

Table 2. Hemodynamic and biochemical variables of myocardial damage and oxygen transport.

Variable	Propofol	Desflurane	p

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CVP Pre	75	72	0.11
NT-ProBNP pre	846.3	1283.5	0.35/0.92
CPR pre	4.71	3.03	0.29/0.94
CKMb pre	13.11	1.95	0.12/0.08
CVS 24h	69.1	71.5	0.29
NT-ProBNP 24h	2338.9	2744.5	0.58/0.9
CRP 24h	146.3	149.1	0.83
CKMMB 24h	17.4	16.3	0.7/0.28
Tropo 24h	2.8	7.8	0.25/0.52
Lactate 24h	1.76	1.65	0.59/0.68
Norepinephrine 24h	37%	38%	0.92
LOCS 24 h	30%	20%	0.37
MAP 24h	74	77	0.35
HCT 24h	33.7	32.5	0.23
CVS 48h	71	71	0.87/0.25
CKMMB 48	10.3	7.7	0.47/0.68
Tropo 48h	1.73	2	0.42/0.87
Lactate 48h	1.39	1.31	0.57/0.48
Norepinephrine 48h	40%	20%	0.09
LOCS 48h	23%	13%	0.32
MAP 48h	77.7	79.6	0.47
HCT 48h	31.3	31.3	0.95

CVS: Central Venous Saturation; CRP: C-Reactive Protein; Tropo: Troponin I; LCOS: Low cardiac output syndrome; MAP: mean arterial pressure; HCT: Hematocrit; pre: preoperative.

Table 3. Variations in kidney stage between groups.

AKI 24	**Propofol**	**Desflurane**
0	17	23
%	28.33	40
1	11	5
%	18.33	8.33
2	2	2
%	3.33	3.33
3	0	0
%	0	0
AKI 48		
0	17	20
	28.33	33.33
1	12	9
	20.00	15.00
2	1	0
	1.67	0.00
3	0	1
	0.00	1.67

AKI: Acute Kidney Injury Scale.

There were significant variations in the increase in creatinine and N-GAL in propofol group at baseline values, 24 hours and 48 hours with regard to desflurane group when analyzing internal kidney function variations. Figure 1 and 2.

Figure 1. Variations in creatinine in relation to baseline values, at 24 and 48 hours in each group.

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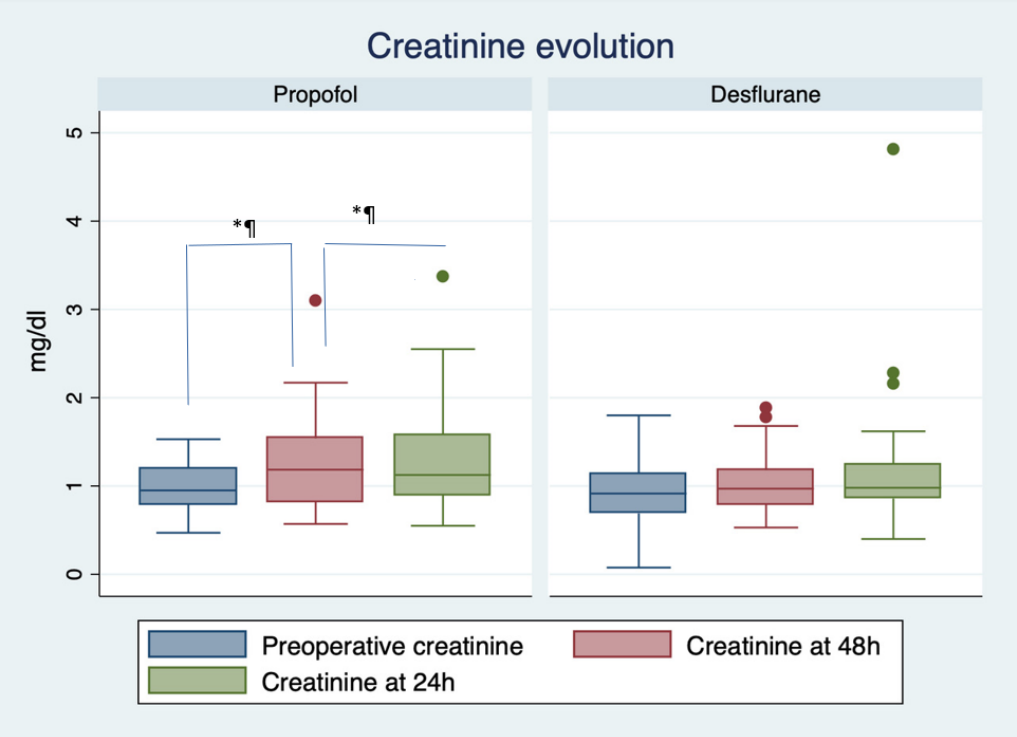
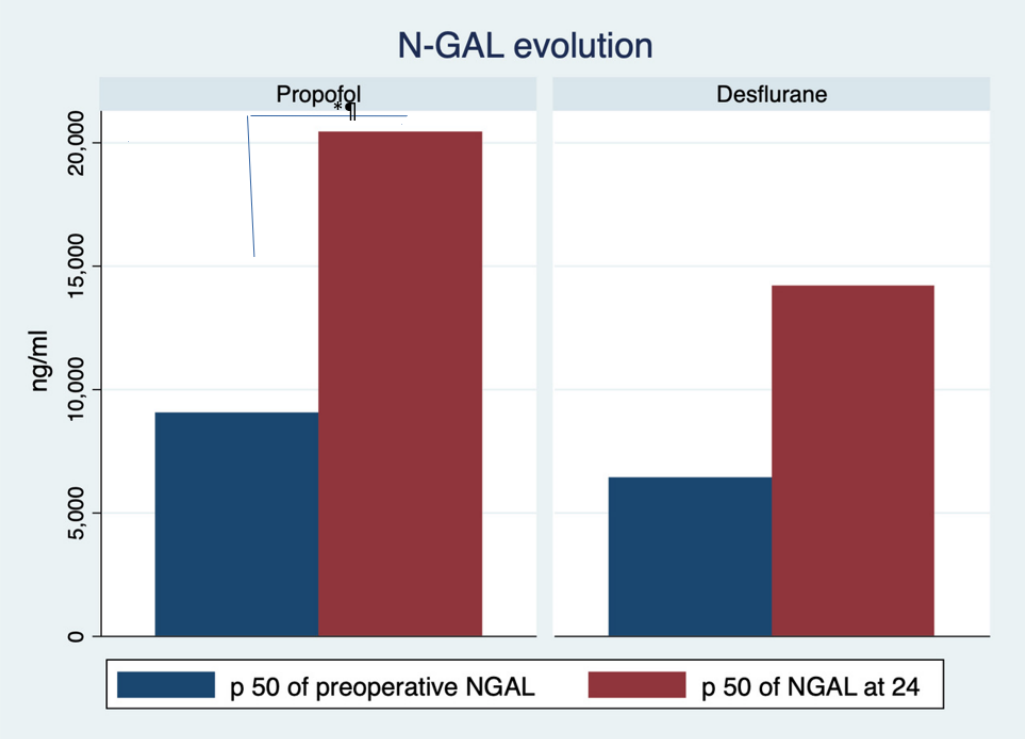


*p<0.05

Figure 2. Variations of urinary N-GAL in relation to baseline values, at 2 hours in each group.



4. Discussion

Intraoperative use of desflurane in aortic valve replacement surgery, in patients without previous kidney pathology, has been shown a nephro-preservative role unlike the use of propofol.

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The use of halogenated drugs has been consistently associated with a cardioprotective role based on the molecular-level effects of pharmacological pre- and postconditioning. Different mediators enzymes, which participate in the SAFE and RISK pathways, are responsible for its final effect [8,12]. The clinical translation of this phenomenon, is a decrease in the incidence of low cardiac output syndrome, through a decrease in biochemical markers of myocardial damage (Troponin I, NTProBNP), which may be reflected in a lower use of inotropic drugs and a shorter hospital stay [2,13]. The sample size in our study was not calculated to assess if there were differences between groups, in relation to myocardial damage and/or lower incidence of LCOS in patients treated with desflurane as a hypnotic compared to propofol. Consequently, they were not found significant differences between them, although with a tendency to reduce damage with the use of desflurane.

Moreover, the role that halogenated hypnotics may play on kidney function has been evaluated in cardiac surgery in several studies. Initially, it seemed that the effect on the kidneys of sevoflurane mediated by compound A, could cause toxicity and kidney failure, recommending avoiding flows lesser than 2 litres/minute during the procedure anesthetic; subsequently, it was shown that its intraoperative use could even benefit patients operated on for heart disease, preserving the function of this organ in the perioperative period of this intervention [6,14]. The use of sevoflurane during the immediate intraoperative and postoperative period of patients undergoing myocardial revascularization surgery, showed levels of N-GAL, at 2 postoperative hours less than in the group that used propofol as a hypnotic drug.

The role by which halogenated drugs achieve this benefit could be multifactorial; firstly, decreased low cardiac output syndrome and better perfusion kidney disease could be related to better nephropreservation [1-4]. Second, if there is a elevation of central venous pressure in relation to right ventricular dysfunction or involvement retrograde that produces an increase in renal venous pressure; will reduce the pressure renal perfusion [15,16]. Third, the mechanisms described for cardioprotection with halogenated share targets that protect the kidneys as in the organic conditioning of the heart; pre and postconditioning renal; enzymes such as Akt and ERK ½ or STAT group, play a mediating role in this protective effect [17].

In our study we found significant intragroup variations in the values of basal creatinine, at 24 and 48 hours in the propofol group, something that did not happen in the group desflurane. In the statistical analysis, the difference between groups at baseline, 24 and 48 hours was of 0.05. Despite not reaching statistical significance, an important difference was shown in the behavior of both groups. In fact, intragroup variations reflect this trend differentiated between each of the groups on renal function.

In our research with the aim of obtaining a greater sensitive and specific marker of renal dysfunction, we evaluated the baseline and postoperative figures of urinary N-GAL in the 30 patients of each group; however, 5 samples from each group were out of range for detection by ELISA techniques due to a high degree of hemolysis generated during extracorporeal circulation, which prevented its analysis [18]. Even so, we found significant variations between the values baseline and postoperative in the propofol group, unlike the desflurane group in which there was no variation.

When interpreting the results of our study, we observed a greater benefit from the use of desflurane in all markers of renal dysfunction compared with propofol use; something that was confirmed in intragroup analysis.

Our results show how the use of desflurane compared to propofol during a low-risk perioperative intervention in cardiac surgery, generates a benefit at the renal level, which is an independent factor of mortality in this group of patients. The importance of keeping desflurane throughout the intraoperative period of aortic valve replacement surgery, including circulation extracorporeal, is the basis of this potential benefit; which has been related in previous studies at cardiac level with drug concentration and the duration of its exposure. Desflurane concentrations used were established for clinical purposes guided

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by hypnosis monitoring, therefore the results are related to the usual use of the drug for this group of patients.

The cause of this effect may be related to the cardioprotective mechanisms of the desflurane. However, the treatment of low cardiac output syndrome was done likewise in both groups without significant variations in central venous saturation, so we assume that oxygen transport was correct regarding to consumption and there were no differences in the mean arterial tensions that would justify these differences. In addition, values of central venous pressure and its possible correlation with retrograde pressure at renal venous pressure neither showed significant variations between groups.

In our opinion, the nephroprotective capacity of desflurane in short-term surgery and with low perioperative risk, suggests an organic effect possibly of greater potency than that achieved with sevoflurane in other studies; something that could be related to the need to maintain levels of expired gas concentration more than twice that required with sevoflurane, in the context of pharmacodynamics of each of these gases; and its action at the brain level to achieve correct hypnosis levels.

One of the biases of our study was the non-randomization of the patients upon being a quasi-experimental design; however, the anesthesiologists were able to decide the type of hypnotic according to their usual clinical practice; in addition, in the statistical analysis we did not find initial differences between the study groups. On the other hand, the working algorithm for the treatment of the syndrome of low cardiac output and for blood volume optimization was similar in both groups, ensuring their homogeneity.

5. Conclusions

The use of desflurane in aortic valve replacement surgery, including the period of circulation extracorporeal, produces a decrease in kidney failure unlike the use of propofol. Mechanisms by which they are mediated may be related to cardioprotection, but according to our results, could be more related to kidney conditioning mechanisms.

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