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Araştırma

Use of Catecholaminergic Inotropic Agents is not an Independent Risk Factor for 30-Day Mortality

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ABSTRACT

Objective: *Low cardiac output syndrome can develop in patients who have undergone open heart surgery. Inotropic drug therapy is being initiated to improve cardiac performance, but these drugs also have significant side effects. The primary aim of this study is to determine the relationship between the use of inotropic drugs and 30-day mortality, however its secondary aim is to determine the independent factors predicting mortality.*

Material and Method: *Our retrospective observational study included 1002 patients undergoing cardiac surgery with cardiopulmonary bypass. Demographic and intraoperative characteristics of patients, use of inotropic agents, postoperative 30-day mortality data were obtained from anesthesia records, postoperative intensive care records and epicrises.*

Results: *Dopamine (n=274: 27.3%), dobutamine (n= 110: 11%) and adrenaline (n=63: 6.3%) were used in indicated number of patients. In the univariate analysis, inotropic drug use was associated with mortality, but multiple regression analysis showed that inotropic drug use was not an independent risk factor for mortality alone. Independent risk factors for mortality were found to be advanced age, hypertension, heart failure, low ejection fraction and preoperative anemia.*

Conclusion: *Our findings showed that inotropic use in perioperative period was not an independent predictor of 30-day- mortality. Although this result is not compatible with studies performed with small number of samples, it is correlated with large-scale patient studies. Independent risk factors for 30-day- mortality were advanced age, hypertension, heart failure, low ejection fraction, and peroperative hemoglobin drop. Our findings are compatible with frequently seen risk factors in research. More progress is needed in this regard.*

Keywords: *inotropy, chronotropy, cardiac anesthesia, low cardiac output syndrome, inotropic agent*

ÖZ

Katekolaminerjik İnotropik Ajan Kullanımı 30 Günlük Mortalite İçin Bağımsız Bir Risk Faktörü Değildir

Amaç: *Açık kalp cerrahisi geçiren hastalarda düşük kardiyak debi sendromu gelişebilmektedir. Kardiyak performansı arttırmak amacıyla inotropik ilaç tedavisine başlanmaktadır, ancak bu ilaçların da önemli yan etkileri mevcuttur. Bu çalışmanın primer amacı, inotropik ilaç kullanımı ile 30 günlük mortalite arasındaki ilişkinin belirlenmesi, sekonder amacı ise mortaliteyi bağımsız predikte eden faktörlerin belirlenmesidir.*

Gereç ve Yöntem: *Retrospektif gözlemsel çalışmamıza kardiyopulmoner baypas ile kardiyak cerrahi geçiren, 1002 hasta dahil edildi. Hastaların demografik ve intraoperatif özellikleri, inotropik ajan kullanımları, postoperatif 30 günlük mortalite bilgileri anestezi kayıtlarından, postoperatif yoğun bakım kayıtlarından ve epikrizlerinden elde edildi.*

Bulgular: *Hastaların 274'üne (%27.3) dopamin, 110'una (%11) dobutamin ve 63'üne (%6.3) adrenalin kullanıldığı gözlendi. Univariate analizde inotropik ilaç kullanımının mortaliteyi etkilediği saptansa da çoklu regresyon analizi sonucunda inotropik ilaç kullanımının mortalite için tek başına bağımsız bir risk faktörü olmadığı görüldü. Mortalite için bağımsız risk faktörlerinin ileri yaş, hipertansiyon, kalp yetmezliği, ejeksiyon fraksiyonu düşüklüğü ve preoperatif anemi olduğu belirlendi.*

Sonuç: *Bulgularımız, perioperatif dönemde inotropik kullanımının 30 günlük mortalite için bağımsız prediktör olmadığını gösterdi. Bu sonuç, küçük örneklemli çalışmalarla uyumlu olmasa da büyük hasta sayılı çalışmalarla koreledir. Otuz günlük mortalite için bağımsız risk faktörleri ileri yaş, hipertansiyon, kalp yetmezliği, düşük ejeksiyon fraksiyonu ve peroperatif hemoglobin düşüklüğü olarak bulundu. Bulgularımız çalışmalarda sık görülen risk faktörleri ile uyumludur. Bu alanda daha fazla ilerlemeye gereksinim vardır.*

Anahtar kelimeler: *inotropi, kronotropi, kardiyak anestezi, düşük kardiyak output sendromu, inotropik ajan*

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INTRODUCTION

One of the major complications seen after open heart surgery is low cardiac output syndrome (LCOS). A cardiac index below 2 L/min/m^2 is considered LCOS and results in insufficient organ perfusion. LCOS is present in 0.2-6% of an adult heart surgery patient population [1]. LCOS may occur with factors that decrease left ventricular preload, such as hypovolemia, tension pneumothorax, positive pressure ventilation, right ventricular dysfunction. It may also occur during increased afterload situations, such as increased systemic vascular resistance, excessive fluid loading, left ventricular distension. LCOS may also be observed in cases, where myocardial protection is not properly provided during cardiopulmonary bypass (CPB) and, in cases with decreased direct left ventricular myocardial contractility such as low ejection fraction, myocardial ischemia, stunning, hypoxia, hypercapnia, and acidosis. After the etiology of LCOS has been identified, goal- directed treatment is started to increase organ perfusion. Support therapy with inotropic drugs is indicated when left ventricular contractility is reduced. Catecholaminergic agents, dopamine, dobutamine, adrenaline are inotropic agents acting on beta, alpha and dopaminergic receptors. In addition, phosphodiesterase inhibitors, calcium sensitizers, vasopressors, vasodilators and mechanical support devices, which act in different ways, can also be used in LCOS therapy. It is said that inotropic drugs in cardiac surgery have positive effects on hemodynamics, as well as increased risk of arrhythmia, myocardial ischemia, hemodynamic fluctuations and various adverse events [2,3].

In studies, inotropic drugs are evaluated together with vasopressor drugs and contradictory results are suggested [4]. Vasopressor drugs are different from catecholamines in terms of their mechanism of action and results. For this reason our research hypothesis is based only on the effects of catecholaminergic drugs dopamine, dobutamine and adrenaline. The primary aim of our study is to investigate the effect of inotropic drug use on 30-day mortality in patients undergoing open heart surgery and our secondary goal is to determine independent factors predicting postoperative 30-day mortality.

MATERIALS and METHODS

This retrospective, observational, and cross-sectional study included 1002 patients who underwent open heart surgery between January 1, 2016 , and January 1, 2017 after receiving the hospital ethics committee approval (Date 26 /06/2016-no. 350). The demographic and perioperative data of the patients were obtained from the electronic information operating system and from anesthesia, and intensive care unit (ICU) follow-up forms. The study included women and men older than 18 years of age who underwent elective coronary artery bypass graft- valve- adult congenital and combined surgeries using CPB. Patients who underwent pediatric cardiac surgery, vascular surgery, off-pump heart surgery, heart transplantation , those using mechanical support devices were not included in the study. Demographic data and comorbidities during the preoperative period were recorded. The data concerning duration of anesthesia, cross- clamping (CC), CBP and 30-day mortality were recorded. The cut-off value for the ejection fraction (EF) was accepted as 40%. Accordingly, EF <40 % and ≥40% were considered as low and normal EF, respectively.

In all patients anesthesia was induced with fentanyl, midazolam, rocuronium and maintained with sevoflurane-midazolam-fentanyl-rocuronium. The CBP was performed using moderate hypothermia with nonpulsatile perfusion flow (2.4 L min^{-1} m^2). Body temperature was monitored with rectal and nasopharyngeal probes. Alpha-stat was used in blood gas management. Priming was carried out with 1500 ml of Ringers lactate solution, 250 mg of albumin and electrolytes. Plegisol (Plegisol, Abbott Lab.) solution (10-15 ml kg^{-1}) was used for cardioplegic arrest, followed by blood cardioplegia at 20 min- intervals. When appropriate conditions are met the pump flow slowly decreased, and the CPB was ended. At this time, the contractility of the heart was assessed with an inspection. During the weaning, the inotropic drugs (dopamine, dobutamine and adrenaline) were started according to the choice of the surgeon and the anesthetist, when poor contractility and hypotension were observed. Phosphodiesterase inhibitors, vasopressin, and noradrenaline were frequently used in patients with heart failure, who underwent cardiac transplantation and/or surgeries with the aid of mechanical support devices. These patients were not included in the study. There-

fore, other inotropic drugs and vasopressors were not used, except dopamine. Dopamine, dobutamine and adrenaline use, their doses and durations of these infusions were recorded intra- and postoperatively. Dobutamine and dopamine exposure was defined as delivery of any dose as long as it was administered for at least three hours in the operating theatre or ICU. Adrenaline exposure was defined as a minimum duration of three hours in the ICU if the dose was <5 μg min^{-1} or any duration if doses of ≥5 μg min^{-1} were used [5].

Statistical Analyses

Statistical analysis was performed using SPSS software (Version 17. 0, SPSS Inc., Chicago, IL, USA). If continuous variables were normally distributed, they were described as mean±standard deviation (SD) (p>0.05 in Kolmogorov-Smirnov test or Shapira-Wilk (n<30)), and if the continuous variables were not normally distributed, they were expressed as medians (IQR). Comparisons between the groups were performed using Student T test or One Way ANOVA for normally distrubited data and Mann Whitney- U test or Kruskall -Wallis test were used for the comparison of data not normally distrubited. The categorical variables between the groups were analyzed by using the Chi square test or Fisher Exact tests. A multiple logistic regression analysis was used to reveal associations between mortality and other measurements, with mortality as an independent variable. The p values below 0.05 were considered statistically significant.

RESULTS

Inotropic agent use was detected in 36. 5% of 1002 patients included in the study. Preoperative EF, peroperative hemoglobin and hematocrit values were found to be significantly lower in patients using inotropic agents, while CC and CPB durations were significantly higher (Table 1, Table 2). Prevalence of atrial fibrillation, cardiac insufficiency and coronary artery disease was significantly higher in the group receiving inotropic drugs (Table 1).

Surgical types of patients using inotropic agents and patients with mortality are presented in Tables 3 and 4, respectively. In 1002 patients, dopamine (n=274:27.3%), dobutamine (n= 110 :11%) and adrenaline (n=63 (6.3%) were used. Mean administration

Table 1. Demographic data of the patients.

	No use of inotropic agent		Use of inotropic agent		
	n	Mean±SD	n	Mean±SD	p
Age (years)	636	56.6±12.8	366	58.3±13.8	0.045
BMI	636	28.1±4.6	366	27.7±5.3	0.221
EF (%)	636	54.3±7.3	366	50.1±9.7	<0.001
Hg (g/dL)[b]	636	14.1±1.7	366	13.5±2.0	<0.001
Htc (%)	636	43.3±14.3	366	41.5±5.5	0.021
Female gender (%)	160	25.2	113	30.9	
Male gender (%)	476	74.8	253	69.1	0.055
ASA					
1	11	1.7	5	1.4	
2	301	47.3	126	34.4	
3	316	49.7	212	57.9	
4	8	1.3	22	6.0	<0.001
5	0	0.0	1	0.3	
DM (%)	142	22.3	80	21.9	
HT (%)	231	36.3	109	29.8	0.875
HPL (%)	111	17.5	40	10.9	0.038
COPD (%)	58	9.1	51	13,9	0.006
CVD (%)	12	1.9	7	1.9	0.021
CRF (%)	10	1.6	8	2.2	1.000
AF (%)	11	1.7	23	6.3	0.471
CHF (%)	74	11.6	86	23.5	<0.001
CAD (%)	468	73.6	184	50.3	<0.001
Other comorbidities	85	13.4	36	9.8	<0.001
					0.108

BMI: Body Mass İndex, Hg: Hemoglobin, Hct: Hematocrit,
ASA: American Society Of Anesthesiologist
DM: Diabetes Mellitus, HT: Hypertension, HPL: Hyperlipidemia,
COPD: Chronic Obstructive Pulmonary Disease,
CVO: Cerebrovasculary Disease
CRD: Chronic Renal Failure, AF: Atrial Fibrillation,
CHF: Congestive Heart Failure
CAD: Coronary Arterial Disease

Table 2. Cross-clemp and operation durations.

	No use of inotropic agent		Use of inotropic agent		
	n	Mean±SD	n	Mean±SD	p
Crosss klemp duration (min)	636	64.4±30.7	366	89.2±41.0	<0.001
CPB duration (min)	636	97.9±39.9	366	136.5±61.6	<0.001
Operation duration (min)	636	291±62.7	366	348.9±98.3	<0.001

Iqr: Interquartile Range
CBP: Cardiopulmonary By-Pass

times of inotropic drugs during intraoperative period were 87±64.8, 106.0±71.9 and 111.3±64.3 mins for dopamine, dobutamine and adrenaline respectively. The durations for inotrop drug use in postoperative period were 28.0±28.8, 37.4±36.2 and 29.4±24.5 mins for dopamine, dobutamine and adrenaline, respectively (Table 5). The mortality rates in patients who received or did not receive inotropic agents were

Table 3. Types of surgeries.

	No use of inotropic agent		Use of inotropic agent		
	n	%	n	%	p
CABG	452	71.0	158	43.1	
MVR	40	6.2	63	17.2	
AVR	37	5.8	27	7.3	
Combined Valve Surgery	18	2.8	39	10.6	
Asc/Arcus Aorta+CABG/ Valve Surgery	50	7.8	44	12.0	<0.001
CABG+Valve Surgery	13	2.0	23	6.2	
Adult Congenital Surgery	26	4.08	12	3.2	

CABG: Coronary Artery By-Pass Grefting
MVR: Mitral Valve Replacement
AVR: Aortic Valve Replacement

Table 4. Types of surgeries and mortality rates.

	Alive		Exitus in 30 days		
	n	%	n	%	p
CABG	576	61.9	34	5.5	
MVR	90	9.7	13	12.6	
AVR	60	6.4	4	6.25	
Combined Valve Surgery	54	5.8	3	5.2	
Asc/Arcus Aorta+CABG/Valve Surgery	81	8.7	13	13.8	<0.001
CABG+Valve Surgery	31	3.4	5	13.8	
Adult Congenital Surgery	38	4.1	0	0.0	

CABG: Coronary Artery By-Pass Grefting
MVR: Mitral Valve Replacement
AVR: Aortic Valve Replacement

Table 5. Durations of infusion of inotropic agents.

	n	Mean±SD	Median
Dopamine (hour)	274	87.0±64.8	70,0
Dobutamine (hour)	110	106.0±71.9	90,0
Adrenaline (hour)	63	111.3±64.3	95,0
PO/ D (hour)	160	28.0±28.2	18,0
PO/DB (hour)	88	37.4±36.2	26,5
PO/A (hour)	25	29.4±24.5	24,0

PO/D: postoperative dopamine infusion duration
PO/DB: postoperative dobutamine infusion duration
PO/A: postoperative adrenaline infusion duration

13.1%, and 3.8%, respectively (p=0.0001). Patients using inotropic agents had a 3.9 -fold (95% CI 2. 4-6.5) higher mortality rates than others (Table 6). When the relationship between the duration of drug use and mortality of patients using an inotropic agent was examined, higher mortality rates were associated with longer use of inotropic agents. In addition, triple use of inotropic drugs were related to higher mortality rates (Table 7).

When significant variables in univariate analyses were included in multiple regression models, advanced age (odds ratio (OR) 1.1, 95% confidence Interval (CI) 1.01-1.1; p = 0.008;), hypertension (p=0.016; OR 3.4; 95% CI 1.3-9.4), heart failure (OR 4.1; 95% CI 1.1-15.9, p=0.043), low ejection fraction (OR 0.93; 95% CI 0.88-0.98, p=0.005) were found to be independent risk factors for mortality. Peroperative anemia was found to be an independent risk factor for mortality as well (OR 0.79, 95% CI 0.66-0.96, p=0.015). In the univariate analysis, inotropic drug use was associated with mortality, but multiple regression analysis showed that inotropic use alone was not an independent risk factor (OR 1.7, 95% CI 0.7-3.8; p=0.216; Table 8).

Table 6. Mortality rate & inotropic agent.

	No use of inotropic agent		Use of inotropic agent		
Mortality	n	%	n	%	p
Alive	612	96,2	318	86,8	<0,001
30-day mortality	24	3,8	48	13,1	3,9 (%95 GA 2,4-6,5)

Table 7. Mortality rates & durations&multiple agent use.

	Alive		30-day mortality		
IQR	n	Median (IQR)	n	Median (IQR)	p
Dopamine (hour)	229	60 (45)	45	97 (142)	<0,001
Dobutamine (hour)	79	80 (75)	31	120 (150)	0,007
Adrenaline (hour)	44	90 (60)	19	135 (150)	0,005
p:Chi-square test	**n**	**%**	**n**	**%**	
Multiple agent use					
One	168	66,1	14	29,2	
Double	64	25,2	13	27,1	<0,001
Triple	22	8,7	21	43,8	

IQR: Interquartile Range; p:Mann Whitney U test

Table 8. Results of logistic regression analysis.

	Explanatory variable	p	Odds ratio	Confidence interval
Response variable	inotropes	0.216	1.7	0.7-3.8
	Preoperative anemia (Hg<13 g/dL)	0.015	0.79	0.66-0.96
30-day mortality	Advanced age	0,008	1.1	1.01-1.1
	Hypertension	0.016	3.4	1.3-9.4
	Heart failure	0.043	4.1	1.1-15,9
	EF	0.005	0.93	0.88-0.98

EF: Ejection Fraction
Hg: Hemoglobin

DISCUSSION

The prominent finding of this study is that catecholaminergic inotropic drug use was associated with mortality in the univariate analysis, but multiple regression analysis revealed that inotropic drug use was not an independent risk factor for 30-day mortality. Independent risk factors for 30-day mortality were found to be advanced age, hypertension, heart failure, low ejection fraction and peroperative anemia.

Most of the randomized controlled trials suggesting increased mortality in patients using inotropic drugs have been performed in patients with heart failure. Use of inotropic drugs in cardiac surgery can be seen at rates up to 90%, depending on the conditions of the patient and the surgical procedure [6]. A retrospective cohort study of 1326 cardiac surgery patients has shown inotropic and vazopressor (norepinephrine, vasopressin, epinephrine, dobutamine and milrinone) exposure is independently associated with mortality either in multivariate logistic regression analysis and propensity score matching [5]. A larger-scale multicenter study has shown perioperative use of inotropic therapy was independently associated with an increased 30-day mortality. In this study 1170 patients received inotropes in the matched cohort, while 28% of them were given a single-drug regimen (dopamine, epinephrine, dobutamine and milrinone), while the remaining patients received a combination of two or more or a sequential treatment with different drugs [7]. In these studies, inotropic drugs and vasopressor drugs were analyzed as usual , and patients with heart failure who used these drug groups more frequently , were included in these studies. Although, in these studies, patients with heart failure presumably created a bias, a comprehensive meta-analysis with large number of patients has found that inotropic use does not increase mortality even in patients group with heart failure [4]. In a meta-analysis which consisted of 28.280 patients receiving inotropes or vazopressors has shown that inotrope/vasopressor therapy is not associated with mortality in the overall population and in the majority of subsettings. These subsettings most frequently included cardiac surgery, heart failure, major non-cardiac surgery, complications of liver cirrhosis, sepsis, and cardiac arrest [4]. Like our study the CAPS-Care study examined the association between inotrope use and outcomes of mortality, where hospitals were classified as high, moderate, low patient load according to inotropic drug use. There were no significant difference among the groups regarding mortality rates [4].

In this study, CC, CBP and whole operation times were found to be longer in the inotropic therapy population. Also we detected that CABG surgery was correlated with a lower incidence of positive inotropic drug use compared with other surgeries (valvular , combined or other). Recent studies have shown that the incidence of inotropic agent use is lower in CABG surgeries than valvular or combined surgeries. Also they have shown that a CC time longer than 90 mins is an independent risk factor for inotropic drugs [4]. Nielsen et al. have shown a CPB time longer than 120 mins is much more correlated with inotropic drug use in original cohort contrary to propensity matched cohort [4]. Solely CABG surgery and off-pump surgeries are weakly correlated with frequency of using inotropic drugs [4]. Another risk factor for inotropic agent use was decreased EF. It has been shown in a study of 97 patients that EF levels under 40% is an independent risk factor for inotropic agent use [9]. In our study we did not calculate the cut- off value for ejection fractions but we demonstrated that the patients with lower EF levels are at a higher risk for inotropic drug use.

As a second outcome of this study; independent risk factors for 30-day mortality were found to be advanced age, hypertension, heart failure and low ejection fraction. It was also observed that the mortality rate increased with the use of multiple inotropic drugs. Of these risk factors, the advanced age and use of more than one inotropic agent have been previously defined as an independent risk factor for 30-day mortality [9]. In a study of 23.016 cardiac surgical patients, the mortality rate was 3.2%, and independent predictors of mortality in the model were age, sex, the New York Heart Association (NYHA) class, urgency of procedure, EF estimate, lipid-lowering treatment, preoperative dialysis, previous cardiac surgery, procedure type, inotropic medication, peripheral vascular disease and body mass index [10]. In another risk prediction study, factors selected as independent predictors in the preoperative isolated coronary bypass AusSCORE model were as follows: age, New York Heart Association class, ejection fraction estimate,

urgency of procedure, previous cardiac surgery, hypercholesterolemia, peripheral vascular disease, and cardiogenic shock. Although there are some common risk factors in the studies, each study have suggested different risk factors. An example of which is the vasoactive-inotropic score (VIS) put forward in recent years. It has been suggested that this scoring system, previously described in pediatric cardiac surgery patients, could also be used in adult cardiac surgery [11]. However this study, as the authors admitted enrolled quite a few patients to recommend this scoring system. The low EF has been shown to be a risk factor for mortality in many studies, and it has been also indicated that the preoperatively elevated left ventricular end-diastolic pressure is predictive of mortality independent of the EF [12]. Another study, especially in the elderly patient group, introduced a 5-meter gait speed as a predictor of mortality [13]. Obviously, a wide variety of parameters have been used to investigate the risk factors predicting postoperative mortality, and even if the same parameters have been mentioned, these parameters are defined differently. For this reason, it is possible to find many different predictive factors in the literature. In our study independent risk factors for 30- day mortality were found to be advanced age, hypertension, heart failure, low EF and anemia. Inotropic use was not found as an independent risk factor. Our findings are often the common risk factors in studies. Apparently, there is a need to move further in this regard.

We should also mention the issue of preoperative anemia. Several studies have shown perioperative anemia as an independent risk factor for 30-day mortality like us [14-16]. Preoperative anemia increased the mortality risk by 3. 4-fold in patients undergoing CABG surgery [15]. Anemia significantly increases EuroSCORE II in cardiac surgery and should be considered to assess cardiac surgery risk [17]. After the anemia has been shown to increase mortality rates , there is consensus regarding the treatment of preoperative anemia in the context of patient blood management [18].

We have some limitations in our study. Although we evaluated 1002 patients, a greater number of patients gave more valuable results in terms of risk assessment. Also the quality of surgery couldn't been assessed, and data related to perioperative morbidity and long- term mortality were missing.

In conclusion, our findings suggest that 30-day mortality is not increased by inotropic use during perioperative period. Altough our findings does not correlate with small sample sized studies, it correlates with larger sample-sized researches. Independent risk factors for 30-day mortality were found to be advanced age, hypertension, heart failure, low ejection fractions and peroperative anemia. Our findings are frequently found risk factors in studies. There is a need to move further in this regard.

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