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Effect of Opium Addiction on Perioperative Needs to Inotropic Agents in Coronary Artery Bypass Surgery: a Case-Control Study.

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Abstract:

Objective: to compare the need to inotropic agents in opium dependent (OD) and non dependent (NOD) patients during the perioperative period in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods and material: 62 male patients up to 75 yrs old scheduled for elective on-pump CABG with ejection fraction>40% were assigned to two groups according to DSM- IV, TR: Opium dependent and nondependent patients. Anesthesia induced and maintained similarly in all patients. During the perioperative period blood pressure(BP),heart rate (HR, central venous pressure (CVP),cardiac output (co),systemic vascular resistance (SVR) ,type and length of inotropes used and the frequency of intra aortic balloon pump (IABP) insertion were monitored and recorded . Paired sample t-test, Independent sample t- test and Chi-Square test were used to compare variables among two groups.

Result: Demographic data showed no significant difference in age, body mass index (BMI), preoperative hemoglobin, ejection fraction (EF) and number of grafts in two groups. Also there was no significant difference regarding the incidence of cardiovascular risk factors and mean blood pressure(MBP). The findings indicated no significant difference in the frequency of inotrope usage[23(74.1%) vs. 25(80.6%); p=0.381] and frequency of IABP insertion [2(6.4%) vs. 3(9.6%); p=0.187] between two groups . But the lenght of the need to inotropes in opium dependent patients was significantly lower in comparison with nondependent patients (26.8± 9.9 vs. 36.1± 17.45; p=0.042).

Conclusion: Although the length of the need to inotropic support in non opium dependent was longer as compared to opium dependent patients, frequency of inotrope need and specific inotrope usage and also frequency of IABP insertion was not different between the two groups.

Keywords: Opium dependent, non opium dependent, coronary artery bypass graft, Inotrope.

Introduction:

Opium abuse is one of the major public health problems and the most common drug abuse in some parts of the world including Iran.[1-3]

There are beliefs about protective cardiovascular effects of opium in some societies or in some papers, while others mention it as an aggravating factor or even a probable risk factor for coronary artery disease (CAD).[2] The major effects of opium are on central and autonomic nervous systems and the bowels, while it has certain influences on other organ systems including respiratory and cardiovascular systems. Hypotension, bradycardia, peripheral vasodilatation or sometimes hypertension and tachycardia are among the cardiovascular effects of opioids.[4] Effect of opioids on ischemic preconditioning and reduction in infarct size was shown in human and rat.[5, 6] Anyway there is no definite answer to many of the questions regarding the cardiovascular effects of opium in opium dependent patients.

In the other hand left ventricular (LV) dysfunction or "low cardiac output syndrome" occurs commonly after cardiopulmonary bypass (CPB), that typically peaks between 4 and 6 hours after surgery, and usually resolves around 24 hrs postoperatively but often necessitating the use of inotropic drugs to achieve an adequate hemodynamic status.[7,8]Therefore many clinicians may treat patients, with inotropic agents at separation from CPB.[9]

There is no sufficient and reliable data regarding the Influences of opium dependence on the hemodynamic condition and need to inotropic agents after CPB and myocardial revascularization surgery. Therefore, it is necessary to perform many studies to evaluate the probable effects of opium.

The aim of the present study was to compare the inotropic needs in opium dependent and non dependent patients during period of weaning from cardiopulmonary bypass and the first postoperative day in patients undergoing coronary artery bypass graft surgery.

Materials and Methods:

Patients

In a prospective case-control study, 62 male patients up to 75 yrs old undergoing isolated CABG in the educational hospitals of Shiraz University of Medical Science(Shiraz, Iran) were enrolled (31 opium dependent and 31 non opium dependent patients).All patients scheduled for elective on-pump CABG with ejection fraction>40% were rcruited during 12 months period. Patients with morbid obesity [body mass index (BMI)>35], emergency surgery or previous cardiac operation, combined operation, severe systemic non cardiac disease other than diabetes and hypertension, such as renal or liver dysfunction were excluded. As the prevalence of opium abuse among female is low, they were excluded too.

Approval of the institutional review board (IRB) and ethics committee of Shiraz University of Medical Sciences was obtained before the study and all of the patients were informed regarding the aims and protocol of the study, and completed the informed consent form.

Study protocol

Baseline characteristics and clinical data of patients including general information, cardiac status and risk factors for coronary artery disease (Hyperlipidemia, Hy-

pertension, Diabetes Mellitus and smoking),history of opium use, clinical and paraclinical characteristics were collected using a questionnaire in the operation room.

According to universally accepted Diagnostic and Statistical Manual for Mental Disorders Fourth Edition, Text Revision (DSM-IV,TR), patients divided into two groups, opium dependent and non-opium dependent.

Current opium users were those who inhaled the smoke of ignited opium and/or ate it in the crude form for at least three times a week and had been used opium within 4 weeks of surgery.

Both types of opium usage are common among the addicts, and distinguishing among them is almost impossible because almost all of the addicts have experienced using both types.

Nonusers included all patients who had never used opium in their lives before surgery.

Preoperative oral administration of chronically taken drugs was continued up to the morning of surgery.

Before induction of anesthesia a peripheral venous catheter was provided and an arterial line was inserted for all patients under local anesthesia and mild sedation. All patients were managed similarly. Anesthesia was induced with midazolam, 0.1 mg/kg, sufentanil, 0.75-1micrg/kg, propofol 1 to 2 mg/kg, and pancuronium 0.1- 0.15mg/kg. After induction of anesthesia and intubation of trachea, a central venous line (in right internal jugular vein) was inserted. Anesthesia was maintained with propofol 100-150 micro g/kg/min and additional dose of sufentanil 0.5-1micrg/kg, midazolam 0.05 to 0.1 mg/kg and pancuronium 0.05- 0.1mg/kg was given as needed. To maintain the blood pressure during the surgery Trinitroglycerin (TNG) was given as required. All CABGs were performed through a median sternotomy and all patients underwent nonpulsatile, normothermic (34-36°C) CPB with intermittent cold blood cardioplegia for cardiac arrest. Perfusion pressure was maintained at 50 to 90 mmHg with pump flow rates of 2 to 2.4 L/min/m2 (Stockert S5, 2010 Germany) throughout CPB. The pump was primed with crystalloid, and serial heamatocrits (Hct) were kept above 0.18 with addition of packed red blood cell, as necessary. At the end of CPB, the patients were actively rewarmed to 37°C while the hematocrit (Hct) kept above 24. Throughout anesthesia blood sugar were checked and maintained bellow 180 mg/dl. Patient received intravenous (IV) morphine 0.1mg/kg slowly before transferring to Intensive Care Unit (ICU).

During anesthesia and operation BP, HR, CVP (Datex Ohmeda S5 2007, USA), cardiac output (co), systemic vascular resistance (SVR) (Novametrix NICO 2001 U.S.A), type and duration of inotropes use, were monitored and recorded by a nurse anesthetist blinded to the study groups. BP was recorded before induction of anesthesia (as pre op. MBP), every 10 minutes during CPB (and its average considered as pump MBP) and every 10 minutes after separation from CPB till end of surgery(the average of all recorded MBP were considered as post pump MBP). During post operative period inotropic support continued if patients was

hemodynamic -ally unstable, otherwise were tapered and then discontinued.

Also duration of anesthesia and operation, pump time, aortic cross-clamp time, usage of lidocaine or electroshock during separation from CPB were also registered.

Initiation of inotropic support was at the discretion of anesthesia care team based on mean arterial pressure (if MBP<55 start first inotrope and if MBP<75 start second one), cardiac output, systemic vascular resistance, and direct visualization of the heart.

Inotropic support was defined as the use of dopamine >5 micro g/kg/min, any dose of epinephrine, norepinephrine, and dobutamine or the insertion of an Intra aortic balloon pump (IABP) during separation from CPB. We focused our analysis on patients receiving any inotrope during separation from cardiopulmonary bypass and the up to 24 hours after operation including any initiated intraoperatively or postoperatively.

Statistical analysis

For continuous variables, the values are expressed as mean ±standard deviation. For discrete variables, the values are expressed as percentages. For continuous variables T-Test was used to asses the differences between two groups and for qualitative variables, Chi-Square test was used. For small sample sizes we used Fisher s exact test. All statistical analysis were performed using SPSS for Windows 16 (SPSS, Chicago, Il, USA). The P-value were considered statistically significant when <0.05.

Results:

A total number of 237 patients were screened, and according to DSM-IV-TR, 62 male patients were enrolled in this study. Demographic data showed no significant difference in age, body mass index (BMI), preoperative hemoglobin, ejection fraction (EF) and number of grafts among two groups. (Table 1)

Table 1: Demographic data of two study groups

	Opium dependent	Non-opium dependent	P. Value
Age (Yrs)	57.54 ± 8.57	60.87 ± 9.75	0.163
BMI (kg/m2)	24.3± 4.5	25.1±4.1	0.471
Hb(gr/dl)	13.6±1.9	13.2±3	0.566
EF(percent)	65.19±98	49.7±14	0.354
Graft (number)	2.1±1.4	2.1±1.4	0.160

Comparative analysis of two groups showed no significant difference about frequency of cardiovascular risk factors such as hypertension (HTN) ,diabetes mellitus (DM) ,hyperlipidemia (HLP) and cigarette smoking .

Table 2: Risk factors for cardiovascular disease in study groups

Risk factor	OD	NOD	P. Value
HTN	13(41.9%)	11(35.4%)	0.397
DM	11(35.4%)	9(29%)	0.393
Hlp	13(41.9%)	10(32.2%)	0.939
Smoking	15(48.4%)	8(25.8%)	0.057

MBP was considered as the main hemodynamic parameter. There was no significant statistical difference between two groups regarding preinduction (P=0.975), post CPB mean blood pressure (P=0.805) and MBP during CPB (P=0.359). Data also demonstrated no significant statistical difference regarding CVP (p=0.125), SVR (p=0.215) and CO (p=0.145) between two groups (Table 3).

Table 3: Hemodynamic parameter in two study groups.

parameter	Opium dependent	Non-opium dependent	P. Value
Preop MBP(mmhg)	101.4 ± 13.4	101.3± 18	0.975
Pump MBP (mmhg)	61.1±11.1	62±18.2	0.805
Post pump MBP(mmhg)	71.7±8.2	69.8±7.9	0.359
CO (lit/min)	5.2±1.83	5.4±1.75	0.145
SVR (dyn.s.cm-5)	1145.5±480.3	999.6±475.8	0.215
CVP (mmhg)	2.9±2.02	4.12±2.7	0.125

Comparing operative parameters including duration of anesthesia and operation, pump and aortic cross-clamp time, showed no significant difference between the two groups (Table 4).

Table 4: Operative parameters of study groups

Time	OD	NOD	P
duration of anesthesia (hrs)	5.9± 1.2	4.7±1.3	0.367
duration of operation (hrs)	4.41± 1.1	3.6±1.19	0.302
Pump time (min)	66.5± 15.9	72± 17	0.196
Cross-clamp time (min)	35.2± 12.1	41± 10.8	0.05

A total of 23 patients (74.1%) in OD group and 25 patients (80.6%) in NOD group needed inotropic support at separation from CPB. Two patient (6.4%) in OD group and 3(9.6%) in NOD group required insertion of an IABP in addition to the pharmacologic support.

We found that there was no significant difference between groups regarding the frequency of inotrope usage and the need to any specific inotrope (Epinephrine, Norepinephrin, Dopamine and Dobutamie). But the duration of need to inotropic support in opium dependent patients was significantly lower in comparison with the nondependent patients (Table 5).

Table 5: Frequency and duration of inptrope use in study groups.

	OD (No,percent)	NOD (No,percent)	P. Value
Patients who need inotrope	23(74.1%)	25(80.6%)	0.381
Patients who didnot need inotrope	8(28.9%)	6(19.4%)	
Frequency of need to 1 Inotrope	19(61.3%)	18(58.1%)	0.370
Frequency of need to 2 Inotrope	4(12.9%)	6(19.4%)	0.361

Frequency of need to 3 Inotrope	0(0%)	1(3.2%)	
frequency of Norepinephrine use	7(22.6%)	10(32.2%)	0.285
Frequency of Epinephrine use	19(61.3%)	22(71.9%)	0.296
Frequency of Dopamine use	1(3.2%)	1(3.2%)	0.754
Frequency of Dobutamine. Use	0(0%)	0(0%)	
Frequency of IABP	2(6.4%)	3(9.6%)	0.187
Duration of inotrope use(hrs)	26.8± 9.9	36.1± 17.45	0.042

Disscusion:

Opium addiction as a common habit is a health problem in many countries including Iran.[1] Routinely DSM- IV-TR criteria are used for diagnosis of opium dependence (OD). We enrolled patients who used opium by oral or inhalational routes as there is much cross over between these methods in the OD patients and also they have similar pathologic or physiologic effects.[1] Anyone who used opium infrequently were not enrolled in the study. Also Due to low prevalence of opium addiction in females, we exclude female patients from the study.

In the present study the prevalence of opium addiction was about 13 % among male CABG patients which is comparable to the findings in general population (2.1-20%) in the previous studies.[11,12]

The major effects of opium are on central and autonomic nervous systems and the bowels, while it has certain influences on other organ systems including respiratory and cardiovascular systems.[13] Ischemic preconditioning which reduces the infarct size is abolished in human and rat by blocking opioid peptide receptors with naloxone.[5] Also according to another study in Iranian drivers significant lower cholesterol level accompanied by lower diastolic blood pressure in opium dependent patient that with other effects of opium can influence the outcome of cardiovascular disease.[14, 15]

The prevalence of opium addiction among patients with myocardial infarction in Iran is higher compared to normal population.[16] This could be due to the belief that opium consumption has a preventive effect against cardiovascular diseases, hypertension and diabetes.[2, 17]

Regarding coronary artery disease (CAD)some studies indicate that opium consumption can modulate related risks of CAD, but other believe that opium could be harmful for CAD.[17, 18] Marmer and coworkers showed in autopsy samples that long exposure to opiates was associated with decreased severity of CAD.(16) But another study conducted by Mohammadi and colleagues in animal model showed that, opium consumption exacerbated the atherosclerosis plaque formation due to hypercholesterolemia.[17] Also Sadeghian et al showed that opium consumption is an important risk factor of CAD.[18] Recent studies have showed that hyperfibrinogenemia and changes in coagulative and fibrinolytic system which may be seen in opium addict patients, can make this patients susceptible to atherogenesis.[19-22]

Considering the above data, there was a question regarding the effect of opium addiction on the state of cardiovascular system and the need to inotrope during weaning from CPB.

To the best of our knowledge this is the first study that assessed the effect of

opium dependence on the inotrope need of CABG operation. In our study, 23 (74.1%) of OD patient and 25(80.6%) of NOD patient need inotropic support during separation from CPB and there was no difference between the two groups(P=0.381).Kenneth et al found that 39% of patients need inotropic support following either CABG or combined CABG and valve surgery with CPB and identify 6 independent predictors (in order of decreasing significance): (1) Wall motion score index (WMSI), (2) combined CABG and mitral valve repair or replacement surgery (3) LVEF < 35% (4) reoperation, (5) moderate-to-severe mitral regurgitation (MR), and (6) aortic cross-clamp time, that may be used to prospectively identify those patients likely to require support at the termination of CPB.(16) The difference in the need to inotrope between the two study could be attributed to the difference management strategy during separation. In our institution a mean blood pressure above 75 mmHg is desired by the surgeons during separation and any patient with MBP < 55 mmHg before separation was put on inotrope.

Comparing the two groups in the present study after controlling the risk factor mentioned in the Kenneth study, we found no significant difference between OD and NOD patient regarding the frequency of need to single, double or triple inotrope or to any specific inotrope during separation from CPB.Therfore the major determinant of the need to inotrope at separation is not opium dependency/no dependency but the CPB itself.

But we found statistically significant difference regarding the length of inotropic support needed following separation from CPB; opium dependent patient required a shorter duration of inotropic support (total time of inotrope use) following CPB to maintain MBP above 75mmHg. This is comparable to the previous studies suggesting protective effects of opium on the cardiovascular system.(8, 23)

Conclusion:

Opium dependency could have protective effects on the cardiovascular system as the length of need to inotropic support following separation from cardiopulmonary bypass in CABG patients is shorter in the opium dependent as compared to non opium dependent patients. Further studies with different inotrope usage strategy at separation from CPB are recommended to elucidate the

Study Limitation

In brief exclusion of female patients from study groups and imprecise history of opium addiction was two major limitation of study. Also we did not use transesophageal echocardiography for assessment of cardiac function during separation from CPB.

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