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Effects of different dose regimens of Milrinone on hemodynamics and Left ventricular systolic function after cardiopulmonary bypass.

Mohamed Abdel Rahman Salem M.D*, Moh. A. Mourad M.D**, Salah Kasem M.D***, Ahmad Abdul Monem Emam M.D# .

*Anesthesia department faculty of medicine Menofeyia university, ** Anesthesia department National heart institute,***Anesthesia department faculty of medicine Ain Shams university, Cardiology department National Heart Institute#.

Abstract

Milrinone can improve myocardial systolic function and hemodynamics by increasing contractility and decreasing afterload, although its appropriate dose regimen has not yet been established for cardiac surgical patients. Despite milrinone effectively increases cardiac function after cardiopulmonary bypass, few studies have specifically evaluated its efficacy during cardiac surgery. We investigated the effects of milrinone on hemodynamics and left systolic ventricular function in cardiac surgical patients immediately after emergence from cardiopulmonary bypass (CPB). Forty five patients undergoing cardiac surgery were studied. They received milrinone (25, 50, or 75 ug/kg) bolus dose over ten minutes followed by 0.25, 0.5, 0.75 ug/kg/min in three patients groups. Heart rate, mean arterial blood pressure, pulmonary capillary wedge pressure, and cardiac index were determined before and after the administration of milrinone and transesophageal echocardiogram were recorded while constant filling pressures were maintained by volume reinfusion from the CPB reservoir. All three doses of milrinone significantly increased CI (2.5, 3.1,3.2 L/min/m^2), HR (98, 96,100 bpm), SV (61,66,67 ml/beat) and EF (61, 66, 66%) after 5 min from the milrinone use ($p<0.001$) and significantly decreased the MAP (80, 81, 82 mmHg), SVR (1127, 965, 928 dyn.s.cm^{-5}) and PVR (183, 165, 157 dyn.s.cm^{-5}) at the same time interval ($p<0.001$) while the PCWP and CVP did not show valuable change. The 50- and 75-ug/kg doses produced significantly larger increases in cardiac index than the 25-ug/kg dose; however, the 75 ug/kg dose did not produce a significantly larger increase in cardiac index than did the 50-ug/kg dose. Two patients receiving milrinone 25 ug/kg developed premature ventricular contractions. The 75-ug/kg dose was associated with a case of ventricular tachycardia treated with xylocaine infusion and three cases of severe hypotension (BP <60 mmHg) requiring phenylephrine infusion and IV fluid replacement. Thus, milrinone improves hemodynamics and left ventricular systolic function when constant loading conditions are maintained.

Refree : Prof ; *Dr. Ibrahin Abd El- Gany*

Introduction

Patients undergoing cardiac surgery often exhibit myocardial dysfunction after cardiopulmonary bypass (CPB) [1-2]. The etiology is multifactorial, with possible causes including incomplete myocardial prote -ction, effects of cardioplegia solutions, global ischemia, and reperfusion injury. The severity and duration of cardiac depression after cardiopulmonary bypass (CPB) corre -lates with the duration of ischemia [3]. Both beta-adrenergic agonists and phospho -diesterase III inhibitors (PDEIII) are frequently used to improve myocardial performance after cardiopulmonary bypass. These two classes of agents exert both their inotropic and vasod -ilatory effects by different mechanisms. Clinical and experimental data have demonstrated that the heart exhibits acute ß-adrenergic receptor desensitiz -ation during CPB; this results in decreased cyclic adenosine monoph -osphate (cAMP) production after stimulation of the ß adrenergic receptors [4-5]. Thus, large doses of ß- agonists may be required to improve contractility, leading to increased myocardial oxygen consumption and the risk of myocardial ischemia and arrhythmias [6]. PDEIII inhibition results in the decrease in left ventricular (LV) wall stress, LV preload reduction, positive inotropic effect, direct coronary vasod -ilatation, and improvement of myocardial function without an increase in myocardial oxygen consumption. This may be of beneficial specifically in patients with limited coronary flow reserve [7-8]. Milrinone is a nonglyc -osidic, nonsympathomimetic drug that increases myocardial cyclic adenosine monophosphate concentration by selective inhibition of cardiac phosphodiesterase fraction III (cAMP-specific). It also increases calcium delivery to the contractile system, thereby increasing myocardial contra -ctility. Milrinone has nearly 20 times the inotropic potency of amrinone [9-10].

Aim of work

The purpose of this study was to investigate whether the adminis -tration of milrinone immediately after aortic cross-clamping improved hemo -dynamics and LV systolic function after CPB in cardiac patients (ischemic or valvular) subjected to open heart procedures and whether any difference would be observed between different milrinone dose regimens.

Patients and Methods

Anesthetic Management

After approval from the local ethical committee and informed written consent, 45 adult patients with either ischemic heart or valvular heart diseases electively scheduled for coronary artery bypass or valve replacement operations requiring CPB were studied. Exclusion criteria included emergency surgery, history of recurrent ventricular tachyca -rdia, obstructive cardiomyopathy, combined CABG-valvular surgery, patients in cardiogenic shock; or history of esophageal disease, precluding the insertion of the transesophageal echocardiographic (TEE) probe. Preoperative routine physical examinations and investigations were done including preoperative ECG, echocardiography, cardiac catheteriza -tion and routine laboratory work, CBC, serum electrolytes, liver and kidney function tests. Preoperative medication consisted of intramuscular morphine 0.1 mg/kg and midazolam 0.15 mg/kg.

Anesthesia was induced with fentanyl (10 mg/kg), midazolam (0.05–0.1 mg/kg), and pancuronium (0.1–0.2 mg/kg), and the patients were ventilated with 100% oxygen. Monitors for patients were included five leads electrocardiography, radial and pulmo - nary arterial catheters (HP Component Monitoring System M1094A; Hewlett Packard, Palo Alto, CA), and TEE. Systolic pressure, diastolic pressure, mean arterial pressure (MAP), pulmo - nary artery pressure, and heart rate (HR) were measured continuously. Cardiac output (CO) was determined by the thermodilution technique with 10 mL cold saline using Criticath ^{TM} SP 5107H TD pulmonary artery catheter (Becton Dickinson critical system). Baseline hemodynamic data and a LV short-axis view were recorded after induction of anesthesia. In all patients, CPB was conducted using a membrane oxygen - ator and mild systemic hypothermia (minimum temperature 34°C). CPB was conducted using a nonpulsatile flow of 2.5–3.5 L/min/m^2. The circuit was primed with 1500 ml balanced salt solution, 250 ml 10% mannitol. Multidose cold crystalloid cardioplegia was used for myocardial protection during CPB. For pH management, ά-stat methodology was used, and activated clotting times was maintained >400 s. Distal anastomoses were usually performed first during continuous aortic cross-clamping, followed by proximal vein grafting during partial aortic occlusion. After the primary surgical procedure, patients were warmed to a temperature of 36.5–37°C.The heart was defibrillated after cardiac reperf - usion if sinus rhythm did not resume spontaneously, epicardial pacing at a rate of 80 bpm was used as needed for sinus bradycardia or atrioventricular conduction disturbances.

Hemodynamic Measurements

The following hemodynamic variables were recorded after induction of anesthesia as a baseline readings: heart rate (HR),mean arterial blood pressure (MAP), mean pulmonary artery blood pressure (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac index (CI). CI was calculated at each CO measurement automatically. All measurements were taken during the expiratory pause phase of the ventilator cycle. Systemic and pulmonary vascular resistance (SVR and PVR), and stroke volume (SV) were calculated from measured variables using standard equations. Patients were weaned from CPB, if SBP did not reach>90 mm Hg a continuous infusion of phenylephrine (10 – 100 ug/min) was started prior to removal of the aortic cross clamp. Patients were randomly assigned to one of treatment groups: group (A) 25 μg/kg bolus+ 0.25 μg/kg/min continuous infusion (n = 15), group (B) 50 μg/kg bolus + 0.5μg/kg/min continuous infusion (n = 15), or group (C) 75 μg/kg bolus + 0.75μg/kg/min continuous infusion (n = 15). Continuous infusions were initiated after a loading dose administered over 10 min. After baseline, the hemodynamic measurements were repeated at 5, 10, and 20 min. Transesophageal echocardiography (TEE) was continuously assessing LV systolic function during milrinone administration and recordings were made simultaneously when hemod - ynamic measurements were obtained.

Transesophageal Echocardiography

The TEE probe (adult multi-plane MPZ 7-4 ALT 5000 transesophageal ultrasound probe connected to an

echocardiography unit – ALT-HDI 5000 model AGMD 835 E) was positioned behind the left ventricle and a short axis view of the left ventricle at the midpapillary muscle level was continuously monitored after induction of general anesthesia. Multiple tomographic cuts with two-dimensional echocardiography was obtained and utilized to calculate left ventricular end systolic volume (ESV), end diastolic volume (EDV) and ejection fraction (EF). The LV endocardium at the apical 4-chamber and apical 2-chamber at the end of diastole was traced to obtain the ED volume, while maintaining a constant left atrial pressure. It was also traced at the end of systole to obtain volume and hence the average EF% could be calculated by the echo-machine. The LV end-diastole was identified by the peak of the R-wave and the end-systole was identified by the minimum LV dimensions at the end of T-wave. A number of techniques are available for estimation of the LV volumes and EF by 2-D echocardiography, the Simpson's method is the one used in this study. It divides the LV cavity into multiple slices (20 sections) of known thickness and diameter D (by taking several short-axis views at different levels along the LV long axis) and then calculating the volume of each slice (area x thickness). The area is π (D x 2)^2. The thinner the slices, the more is accurate the estimation of LV volume.

Statistical Analysis of the present stud

Statistical analysis was perfor - med on hemodynamic data and echoca - rdiographic variables by one-way and two-way analysis of variance (ANOVA) to compare changes within each group and paired Student's test to compare two different groups data. Statistical analysis was conducted using statistical software (SPSS). $P < 0.05$ was considered statistically significant, and all data are expressed as mean ± SD.

Results

Demographic and preoperative data for the milrinone groups are described in patients undergoing coronary artery bypass grafts, aortic valve replacement, and mitral valve replacement as seen in table (1) were studied. There were no significant differences in age, gender, weight, height, body surface area, aortic cross-clamp time, or CPB time. Likewise, patients had similar incidences of diabetes mellitus and hypertension, were receiving similar preoperative medications, had the same baseline routine laboratory work and underwent similar operative procedures.

Table (1) Preoperative and demographic data:

Parameter	Group A	Group B	Group C
Age (y)	49±5	48±6	50±7
Gender M/F	8/7	10/5	11/4
Weight (kg)	78±8	75±10	80±7
Height (cm)	176±12	174±15	178±14
BSA (m^2)	1.89±0.11	1.90±0.13	1.87±0.09
Cross clamp time	56±13	62±11	58±15
CPB time (min)	118±31	132±22	126±25
Operation CABG	7	4	5
AVR	3	4	4
MVR	5	7	6

BSA= body surface area, CABG= coronary artery bypass grafting, MVR= mitral valve replacement, AVR=aortic valve replacement.

Table (2) Hemodynamic data in different Milrinone groups:

Parameters	Baseline	5min	10min	20min
HR (bpm)				
A	92±7	98±9*	97±12	96±13
B	89±10	96±12*	93±11	93±9
C	92±11	100±8*	99±13	98±11
MAP (mmHg)				
A	87±10	80±12*	79±11	81±8
B	89±9	81±10*	80±10	82±6
C	91±11	82±11*	80±8	81±9
MPAP(mmHg)				
A	23±6	22±5	22±6	23±6
B	24±4	22±7	23±6	24±8
C	25±5	23±4	24±5	26±7
CVP (mmHg)				
A	11±4	10±3	10±3	11±5
B	10±4	9±3	10±4	10±4
C	10±3	9±4	9±3	10±3
PCWP(mmHg)				
A	11±3	11±3	10±4	10±5
B	12±2	12±4	11±3	11±3
C	13±5	12±2	12±4	12±4
CI (L/min/m^2)				
A	2.0±0.1	2.5±0.1**	2.8±0.2*	2.7±0.1
B	2.2±0.2	3.1±0.2**	3.5±0.1*	3.6±0.1
C	2.3±0.2	3.2±0.3**	3.5±0.2*	3.6±0.2
SVR(dyn.s.cm^{-5})				
A	1530±139	1127±122**	985±154*	1058±147
B	1454±175	965±138**	860±122*	814±133
C	1408±154	928±124**	821±136*	788±153
PVR(dyn/s/cm^{-5})				
A	240±36	183±31**	189±38	202±35
B	208±29	165±24**	176±29	183±31
C	216±33	157±35**	161±28	170±39
SV (ml/beat)				
A	56±9	61±6*	62±7	62±4
B	59±6	66±3*	67±4	67±5
C	58±7	67±5*	68±7	69±7

HR=heart rate, MAP=mean arterial pressure, MPAP=mean pulmonary artery pressure, CVP=central venous pressure, PCWP=pulmonary capillary wedge pressure, CI=cardiac index, SVR=systemic vascular resistance, PVR=pulmonary vascular resistance, SV=stroke volume, **P <0.001, *P <0.05.

The changes in hemodynamic variables in each group after emergence from CPB are summarized in table (2). A baseline recordings, showed no significant difference in hemodynamic variables among all groups.

In all milrinone groups, HR significantly increased from baseline at 5 min (10%) but other time intervals at 10 and 20 min did not show significant change ($p<0.05$). Two patients in group A developed ventricular premature contractions after the start of the milrinone infusion and one patient in group C developed a run of ventricular tachycardia which was treated by xylocaine 1mg/kg bolus dose followed by 50 ug/kg/min continuous infusion.

Mean arterial pressure (MAP) was significantly decreased after 5 min (8-12%) and $p <0.001$ without significant change in the other time intervals. Three patients in group C developed severe hypotension after the

bolus dose (<60 mmHg) that required phenylephrine infusion, blood from the pump-oxygenator, and IV fluid. The median total volumes (in milliliters) of blood and IV fluid transfused during the first 10 min after the milrinone loading doses were: 450 ml (range, 410–500 ml), 630 ml (range 450–800 ml), and 860 ml (range 380–1040 ml), respectively, for the 25, 50, and 75 ug/kg doses (P = NS). There were no other significant changes in mean arterial pressure relative to baseline at any time in any of the three groups.

Likewise, there were no significant differences between the three dose groups at any time. No significant changes in MPAP, PCWP, or CVP were observed in milrinone groups.

Table (3) Echocardiographic data in different milrinone groups

parameters	Baseline	5 min	10 min	20 min
EDV (ml)				
A	108±5	99±4**	97±5	97±4
B	112±6	100±5**	96±4	95±4
C	110±5	101±4**	96±6	98±3
ESV (ml)				
A	51±4	38±5**	35±4	35±5
B	52±4	34±4**	30±5	29±3
C	52±3	34±3**	28±6	26±4
EF%				
A	52±4	61±3**	63±4	63±3
B	54±3	66±4**	70±5*	71±3
C	53±4	66±3**	71±4*	72±5

EDV=end-diastolic volume, ESV=end-systolic volume, EF=ejection fraction, **p<0.001, *p<0.05.

Milrinone significantly increased cardiac index at all three groups. It is significantly increased (20% in group A and 32% in group B and C) from the baseline. In comparison, between the milrinone groups, CI was significantly higher at 5 (P<0.001) and 10 min (p<0.05) in all milrinone groups then maintained at 20 min. There were no significant differences between the 50- and 75-ug/kg doses at any time point. In the 25-ug/kg dose group, cardiac index significantly increased relative to baseline by the 5-min measurement and remained significantly increased until the 20-min measurement. In the 50 and 75-ug/kg dose group, cardiac index was significantly increased relative to baseline at all measurements.

Pulmonary vascular resistance and systemic vascular resistance significantly decreased (14% and 23% respectively) from the baseline at 5 min (p< 0.001) and 10 min (p<0.05) for SVR only. SV was significantly increased after 5 min (p<0.05).

Echocardiographic variables are presented in table (3). There were no significant differences in EDV, ESV or EF baseline readings between the milrinone groups. EF significantly increased from the baseline at 5 min in all groups (p<0.001) and 10 min in group B and C (P<0.05). EDV and ESV were significantly decreased at 5min (P<0.001) in all milrinone groups.

Discussion

Weaning from CPB after cardiac surgery is a major problem in the patient with congestive heart failure or ventricular dysfunction. $ß_1$-adrenergic receptor down-regulation may contribute to difficulty in weaning from CPB with catecholamines and vasodilators. Since the PDE III inhibitor can bypass $ß_1$-adrenergic receptors to increase cAMP and improve myocardial contractility [11,12,13] . After emergence from CPB in cardiac surgical patients presented in this study, milrinone loading doses (25, 50,75 ug/kg) plus continuous infusion (0.25, 0.5,0.75 mg/kg/min) were shown to effectively improve hemodynamics and LV systolic function. These regimens were associated with significant increase in HR and a significant decrease in MAP when preload as assessed by PCWP and EDV was maintained constant. This study also confirmed that milrinone increases cardiac index in a dose-dependent manner and decreases both PVR and SVR in cardiac surgical patients. The 50- and 75-ug/kg doses were more efficient than the 25-ug/kg dose. The 75-ug/kg dose produced no greater increase in cardiac index than the 50-ug/kg dose, on the other hand, it was associated with a single case of ventricular tachycardia. Thus, it is recommend that 50 ug/kg be used as the initial milrinone bolus dose in cardiac surgical patients after cardiopulmonary bypass. The IV use of milrinone has been reported to increase CI and decrease LV preload and afterload in patients with chronic heart failure [17]. Previous studies conducted after cardiac surgery demonstrated that a loading dose plus continuous infusion of milrinone successfully increased CO with a decrease in PCWP and systemic vascular resistance, which indicates that milrinone is effective in emergence from CPB [14,15,16]. In another study, Butterworth et al. also demonstrated that a 50-ug/kg bolus dose of milrinone increased CI after CPB [18].

Although thermodilution CO facilitates the clinical assessment of cardiac function, it is dependent on LV preload, afterload, and myocardial contractility, all of which may be altered under milrinone administration. Taking this into account, TEE analysis of LV function was performed. Changes in EDV by two-dimensional echocardiography reflect the change in LV preload. This study demonstrated that EDV was significantly reduced with milrinone use [15].

In previous reports, milrinone has been shown to reduce ventricular afterload. These trends toward decrease in LV afterload were observed in the present in all groups as documented by the significant decrease in systemic vascular resistance [16]. The ejection fraction was significantly increased with milrinone in 5 and 10 minutes in all groups which suggested a positive inotropic effect of milrinone.

There are limitations to the present study. The patients undergoing different kinds of operations, and differences of the disease pathology at the cellular level and the responses to milrinone must be considered in interpreting the results of this study. However, no significant difference was observed in the demographic data among the study groups, and the bias due to the variety of the operations is thought to have minimum influence on the results. Also, in the search for an optimal dosage regimen of milrinone in cardiac surgical patients, the need for vasoconstrictors should be evaluated.

In conclusion, milrinone administered as a loading dose plus a continuous infusion effectively

increased CI, EF and HR and decreased MAP, PVR and SVR immediately after emergence from CPB. A 50-ug/kg dose of milrinone is effective and achieves adequate hemodynamics with minimal side effects as compared with 25- and 75-ug/kg doses. Only one patient demonstrated severe arrhythmia after receiving milrinone in a dose of 75 ug/kg.

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تأثيرات الجرعات المختلفة من عقار ميلرينون علي ديناميكية الدم و وظيفة البطين الأيسر الأنقباضيه بعد جراحة القلب و الصدر

محمد عبد الرحمن سالم* محمد أحمد مراد صلاح قاسم*****

أحمد عبد المنعم امام #

أقسام التحذير (جامعة المنوفية)* . (جامعة عين شمس)* . معهد القلب القومي **،#**

يستطيع ميلرنبون تحسين الوظيفة الأنقباضيه للقلب و أيضا ديناميكية الدم و ذلك عن طريق زيادة انقباض العضلة و تقليل المجهود عليها وعلي الرغم من ان جرعة العقار لم تتحد بعد لمرضى جراحات القلب فان ميلرينون يزيد وظائف القلب بعد عمل جهاز القلب والرئه الصناعية.

و هناك القليل من الدراسات المتخصصة التى تناولت تأثير المستحضر أثناء جراحة القلب وقد تناول البحث دراسة تأثيرات الميلرنيون علي وظائف البطين الأيسر الانقباضية ودنياميكية الدم في مرضي جراحات القلب بعد خروجهم مباشرة من جهاز القلب والرئه الصناعية.

وقد تناول البحث دراسة 45 حالة جراحة قلب قسمو الي ثلأث مجموعات . وقد اعطي المرضى جرعة كبيرة خلأل عشر دقائق (25. و75.50 ميكروجرام /كم/ دقيقة)ثم تبعتها جرعات (25. و75.50 ميكروجرام /كم/ دقيقة) وتم قياس عدد دقات القلب ، متوسط ضغط الدم ضغط الشعيرات الرئوية المنحشر . ومعامل القلب قبل وبعد إعطاء الميلرنيون . وتم أيضا عمل موجات صوتية للقلب عن طريق المرئ مع المحافظة علي ثبات الضغوط المالئة بواسطة إعادة الحقن المتواصل من خزان جهاز القلب والرئه الصناعية .وقد أثبتت الدراسة ان كل الجرعات الثلأث من الميلرنيون تؤدى الى زيادة ذات دلاله إحصائية فى معامل القلب (2.5 و3.1 و 3.2 لتر /دقيقة /م2) ، عدد دقات القلب(100،98،96 دقة /دقيقة) ،حجم الدم المندفع مع كل نبضة (61،66،67 مللتر / دقة) ،معامل الضخ (61،66،66 %) بعد 5 دقائق من استخدام ميلرنيون وأدت ايضا الى نقص واضح في متوسط الضغط الشرياني (80،81،82 مم زئبق) ،المقاومة العامة للأوردة (1127،965،928 دين /سم-5 مساحة) والمقاومة الطرفية للأوردة (183،165،157 دين /سم-5 مساحة بينما لم يتأثر ضغط الشعيرات الرئوية المنحشر والضغط الوريدي المركزي .وقد لوحظ ايضا ان الجرعتين 50،75 ميكرو جرام /كم قد ادتا الي زيادة ملحوظة ذات دلاله إحصائية في معامل القلب اكثر من جرعة 25 ميكروجرام /كم وان الجرعة 75 ميكرو جرام /كم لم تسبب زيادة كالتي أحدثتها جرعة 50 ميكروجرام /كم .وقد تعرض حالتان فقط من الذين تناولوا جرعة 25 ميكرو جرام /كم للتذبذب البطيني بينما تعرض مريض واحد فقط من الذين تناولوا جرعة 75 ميكروجرام / كم وقد تم علاجهم باستخدام محلول الزيلوكايين 2% وتعرض ثلأث حالأت من الذين تناولوجرعة 75 ميكروجرام / كم لهبوط حاد في الضغط (اقل من 60 مللتر /زئبق) وقد تم علاجهم بمحلول فينيل افرين والمحاليل التعويضية.

ونستخلص من هذا البحث ان الميلرنيون يحسن ديناميكية الدم و وظيفة البطين الأيسر الأنقباضية في حالة ثبات التحميل علي عضلة القلب أثناء جراحة القلب .