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RESEARCH ARTICLE

COMPARISON BETWEEN THE EFFECT OF AMIODARONE AND LIDOCAINE WITH MAGNESIUM SULFATE ON OCCURRENCE OF REPERFUSION VENTRICULAR FIBRILLATION AFTER AORTIC CROSS CLAMP RELEASE ON AORTIC VALVE SURGERY.

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Key words:-
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Abstract

Background:Reperfusion ventricular fibrillation (VF) after aortic cross-clamp (ACC) release is one of the most common complications after Aortic valve surgery.

Materials and methods:Eighty seven patients who had undergone Aortic valve surgery were assigned randomly to three groups (29 patients each). The lidocaine group received lidocaine with magnesium sulfate (mgso4) (100 mg lidocaine and 2g mgso4) in 25 ml isotonic saline, the amiodarone group received (300 mg amiodarone) diluted in 25 ml of an isotonic saline, and the control group received 25 ml normal saline by a pump circuit 3 min before ACC release. Anesthetic management, weaning protocol from cardiopulmonary bypass, were standardized. All the patients were monitored after the release of ACC and VF were recorded.

Results:Incidence of VF after release of ACC was lower in the lidocaine with mgso4 group compared with the amiodarone and control group [6 (20.7%), 8 (27.6%) vs. 12 (41.4%)] but there was no statistically significant difference between all groups (P = 0.215). Also, the incidence of an atrioventricular block and bradycardia after release ACC was higher in the lidocaine mgso4 group compared with the amiodarone and control groups [7 (24.1%) vs. 4 (13.8%) and 3 (10.3%), respectively)] but there was no statistically significant difference between all groups (P = 0.331).

Conclusion:The administration of lidocaine with mgso4 before the release of ACC reduced the incidence of VF. However, the administration of Lidocaine with mgso4 was associated with more transient atrioventricular block.

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Introduction:-

The occurrence of ventricular fibrillation (VF) after removal of the aortic cross-clamp in patients operating cardiovascular surgical procedure has been accounted for to be somewhere in the range of 45% and 100%. **(Samantaray et al., 2010)**

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Numerous mechanisms have been suggested to give an explanation for the elevated incidence of VF, as well as ischemia-mediated increases in reentry, automaticity, and reperfusion injury. **(Kaplinsky et al., 1981)**

VF may lead to greater than before myocardial oxygen consumption, enlargement of the ventricle with consequential wall tension increase, and myocardial tissue acidosis. **(Lockerman et al., 1987)** These changes may be especially obvious within the hypertrophied ventricle when the mean arterial blood pressure is lower than 50 to 60 mm hg. **(Spadaro et al., 1982)**

Despite the fact that VF is thought to adversely have an effect on the heart, the ‘‘gold standard’’ management is internal direct-current shock, which could be harmful. animal models using monophasic damped sine waveform shocks suggest that defibrillation leads to diminished myocardial performance and microscopic damage to myocytes as well as the injury is more obvious with frequent shocks with a short time between shocks. **(Yamaguchi et al., 2002)**

From these data, the prevention of reperfusion VF or a reduction in the defibrillation attempts needed to discontinue VF could be of advantage in saving myocardial function after cardiopulmonary bypass (CPB). lidocaine, a class IB (Na channel blocking) anti-arrhythmic medication, has a long history of use in cardiac surgical procedure for the prophylaxis of VF. many studies have demonstrated that its effectiveness in preventing VF and reducing the shocks needed to defibrillate VF. **(Ayoub et al., 2009)**

Intravenous amiodarone (class III antiarrhythmic drug) has many mechanisms of action, together with blockade of sodium, potassium, and calcium channels, moreover as beta and alpha-adrenergic antagonism. **(Sarkozy & Dorian, 2003)**

Alternative studies have demonstrated amiodarone to enhance the VF response to shocks. **(Petrovic et al.,1998)** Two modern studies have weighted amiodarone for VF prophylaxis after aortic cross-clamping with mixed outcome. **(Samantaray et al., 2010)**

The goal of the present study was to evaluate whether amiodarone or lidocaine with magnesium sulfate was superior to placebo for the prevention of VF after aortic cross clamp removal in patients undergoing aortic valve surgery.

Materials And Methods:-

This randomized controlled trial study was conducted in Beni Suef university Hospital from 2/2016 to 2/2018 after approval by the internal ethical committee. Written informed consent was taken from all patients before the start.

Patients were eligible for inclusion if they were undergoing an elective aortic valve procedure that was expected to include cross clamping of the aorta. Patients excluded from the study who had history of treatment with digoxin, amiodarone, or lidocaine (including cardiopulmonary resuscitation). Also, patients had Contraindications to amiodarone (sick sinus syndrome, atrioventricular conduction abnormalities, thyroid disease, interstitial lung disorders, renal or liver disease, and known allergic or toxic reactions to amiodarone) or patients with Combined cardiac surgery and emergent operation.

Patients were randomly assigned to three groups in a 1:1:1 fashion. Group A received 300 mg of amiodarone diluted with normal saline to 25ml, group B received 5ml of lidocaine 2% (100 mg) and 2g magnesium sulfate (25ml), and group C (control group) received 25 ml normal saline by the way of pump circuit, 3 minutes before aortic cross clamp release. All study drugs were prepared by a research pharmacist and diluted to 25 mL total volume. Anesthesiologists, surgeons, and CPB perfusionists were strictly blinded as to the content of the syringes.

Procedure

Patients’ baseline characteristics will include age, sex, weight and the patients’ echocardiographic information included concomitant valve disease and left ventricular ejection fraction (LVEF). Standard clinical protocol was used for all patients. Complete blood count, a standard coagulation profile and electrolytes was performed a day before surgery.

All patients were monitored with pulse-oximeter, invasive blood pressure (IBP) device, central venous pressure (CVP), and electrocardiography (lead II toV5). Premedication was midazolam 2-3 mg one hour before surgery.

General anesthesia was induced with fentanyl 5µg/kg, midazolam 0.1-0.2 mg/kg, and atracurium 0.5 mg/kg, and anesthesia was maintained using fentanyl 2 µg/kg before sternal incision, isoflurane 1 vol %, and atracurium 5 µg/kg/min.

The operation was performed through a standard median sternotomy with cardiopulmonary bypass (CPB) (Sorin C5) machine with a flow rate of 2.4-4.2 l/m^2 and moderate hypothermia at 30°C. CPB was instituted with a standard kit and a hollow-fiber membrane oxygenator (Sorin). The CPB circuit was primed with Ringer's acetate and carefully de-aired. Standard cannulation consisted of arterial cannulation in the distal part of the ascending aorta and a 2-stage venous cannula inserted into the right atrium and the inferior vena cava. Myocardial preservation consisted of either anterograde or intermittent antegrade and retrograde cardioplegia. Cardioplegia was repeated every 20 to 30 minutes or on the return of electrical activity of the heart.

Patients were randomly assigned to three groups. Group A received 300 mg of amiodarone diluted with normal saline to 25 ml, group B received 25 ml of lidocaine 2% (100 mg) and 2 g magnesium sulfate (25 ml), and group C (control group) received 25 ml normal saline by the way of pump circuit, 3 minutes before aortic cross clamp release.

Intraoperative variables included ACC time, CPB time, cardioplegic volume, and two samples for electrolyte and arterial blood gas (ABG) values. Patients weaned from CPB when rewarmed to core temperature of at least 37°C and were hemodynamically stable. Electrolyte and ABG values tested once more after weaning from CPB. Whenever the patient's rhythm will be VF after ACC release, the antiarrhythmic drug was reused and the patient was treated with internal biphasic truncated exponential direct current (DC) shock with stepwise increasing energy at the frequency of 20 J. Furthermore, in spite of normal ABG and serum level of electrolytes, if this did not lead to a stable rhythm, a 30-J shock was given after the administration of another dose of antiarrhythmic drug. Reuse of antiarrhythmic drug means another single dose of lidocaine in group A, amiodarone in group B, and lidocaine and magnesium sulfate in group C. It should be mentioned that surgeons were blinded to the type of drugs during this study.

Outcome Measurements

Patient demographics were recorded and included age, gender, weight, left ventricular ejection fraction, duration of CPB, duration of aortic cross clamping, volume of cardioplegia and duration of operation. The primary outcomes were compared among the 3 study groups including the incidence of VF after aortic cross clamp removal and the second outcomes were the number of defibrillations required to terminate VF.

Sample Size

In this study there were three independent groups, the significance of the differences in three sample means is being evaluated using F-test (ANOVA). The alpha level is α=0.05, effect size =0.39 and the power is 0.90. Using G Power, for the total sample size at f=3.1 and degree of freedom=2 was 87 patients in the three groups.

Statistical Methods

Data were collected, entered and analyzed by IBM SPSS version 22 for windows. Categorical variables were analyzed using chi-square tests or Fisher exact test (where appropriate), whereas continuous variables were compared using analysis of variance or Kruskal–Wallis tests (where appropriate regarding normality tests). All statistical tests were 2-sided with the alpha level set at 0.05 for statistical significance. P-value was considered significant at less than 0.05).

Results:-

A total of 87 patients were enrolled in the trial. There were 29 patients in group A, 29 patients in group L, and 29 patients in group P. Base line characteristics of patients under the study were summarized in table (1), bypass criteria in table (2), Impact of using the lidocaine, amiodarone and saline on arrhythmia and need of DC shock in table (3) and troponin level after 24 hours in figure (1).

Table 1:-Comparison between the three groups regarding the base line characteristics of patients under the study

Characteristics	Groups			P-value
	Lidocaine	Amiodarone	Control	

Age Mean ±SD	35.6±13.3	36.7±14.8	34.1±15.7	0.801
Gender (No &%) Male	19	19	22	0.617
Female	10	10	7	
Weight Mean ±SD	79.3±12.2	79.8±9.7	84.5±11.8	0.164
Ejection fraction Mean ±SD	59.1±8.4	55.8±9.3	58.2±7.6	0.315
Main Valve lesion (No &%) Aortic stenosis	8(27.6)	6(20.7)	6(20.7)	0.771
Aortic regurgitation	21(72.4)	23(79.3)	23(79.3)	

Data of Age, weight and ejection fraction presented as mean and standard deviation(SD) and of gender and main valve lesion as number and percentage

Table 2:-Comparison between the three groups regarding bypass criteria

Criteria	**Mean ± SD**	**P-value**	**95% C.I for Mean**	
			Lower Bound	**Upper Bound**
ACC				
Lidocaine	142.8±49.2		124.1	161.5
Amiodarone	133.1±19.4	0.092	125.7	140.5
Control	123.2±24.9		113.7	132.6
CPB Time				
Lidocaine	174.1±60.9		150.9	197.3
Amiodarone	161.3±24.8	0.091	151.8	170.7
Control	149.9±28.6		139.1	160.9
Cardioplegia volume				
Lidocaine	2322±752		2033	2610
Amiodarone	2168±328	0.298	2038	2298
Control	2105±541		1941	2269
Length of operation				
Lidocaine	264±60		240.8	287
Amiodarone	258.6±28.9	0.392	247.6	269
Control	248.5±32.9		236	261

Data presented as mean and standard deviation(SD)

Table 3:-Impact of using the lidocaine, amiodarone and saline on arrhythmia and need of DC shock

Outcome	Groups			P-value
	Lidocaine **(No &%)**	Amiodarone **(No &%)**	Control **(No &%)**	
Incidence of VF after ACC release	6(20.7)	8(27.6)	12(41.4)	0.215
Incidence of Bradyarrhythmia or Heart block	7(24.1)	4(13.8)	3(10.3)	0.331
Need of DC shock				
once	4(13.8)	7(24.1)	10(34.5)	0.421
twice	2(6.9)	1(3.4)	2(6.9)	
Amount of joules				
Take 20	4(13.8)	7(24.1)	10(34.5)	
Take 50	2(6.9)	1(3.4)	2(6.9)	0.421

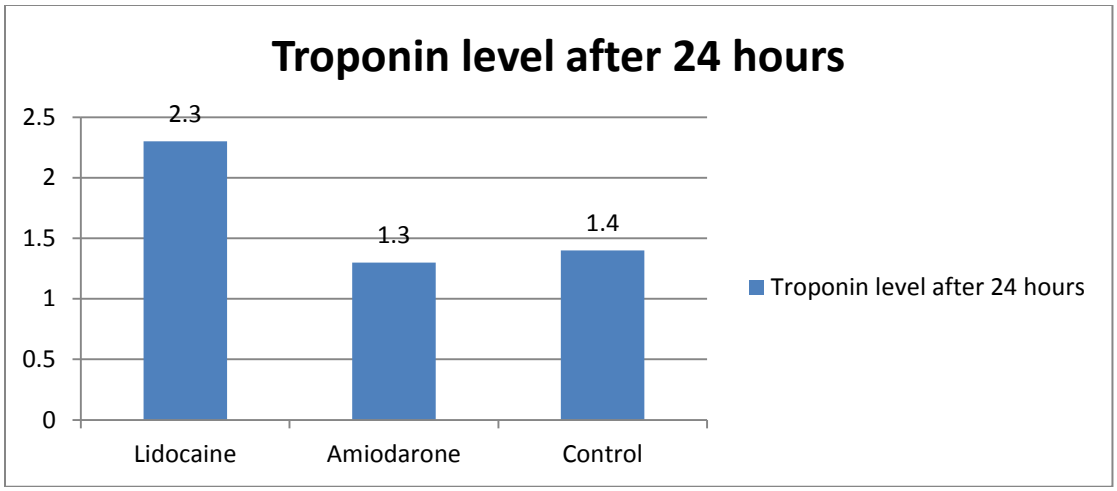

Figure 1:-Comparison between the three groups regarding troponin level after 24 hours

Discussion:-

In this trial of patients undergoing aortic valve procedures, neither amiodarone nor lidocaine given 3 minutes before aortic cross clamp removal decreased the incidence of VF. However, amiodarone, but not lidocaine, decreased the number of shocks required to terminate VF.

Many studies have shown lidocaine to decrease the reperfusion VF incidence when compared with control groups. **(Ayoub et al., 2009)(Fall et al., 1987)(Praeger et al., 1988)(Samantaray et al., 2010)**

All of these studies were performed in patients undergoing CABG. Thus, the current trial differs from these studies in that we included aortic procedures. Our study also was similar with two of previous studies and differed from other studies in terms of lidocaine dosing. Two of the previous studies used doses of 100 mg of lidocaine similar to us , **(Ayoub et al., 2009 (Baraka et al., 2000)** two studies used doses of 200 mg of lidocaine, **(Praeger et al., 1988) (Samantaray et al., 2010)** and one study administered 2 mg/kg of lidocaine. **(Fall et al., 1987)**

Praeger et al. showed that the incidence of VF was reduced to less than 33% with treatment with 200 mg of lidocaine intravenously 3 minutes before aortic cross clamp release. **(Praeger et al., 1988)**

Samantaray and colleagues randomized 34 patients undergoing CABG to receive 150 mg of amiodarone or placebo before aortic cross clamp removal. The incidence of VF in the amiodarone group was 18% versus 65% in the placebo group (P = 0.01). **(Samantaray et al., 2010)**

In a large trial, Ayoub and colleagues randomized 120 patients undergoing CABG to receive 150 mg amiodarone, 100 mg lidocaine, or placebo 2 minutes before removal of the aortic cross clamp. They found that VF incidence was higher in the groups receiving amiodarone or placebo versus the group receiving lidocaine (48% vs. 45% vs. 20% respectively, P = 0.031). However, they found the energy required to terminate VF was lower in the patients receiving amiodarone versus the controls (16 ± 7 J vs. 25 ± 8 J; P= .023). **(Ayoub et al., 2009)**

The dose of amiodarone used in this study was significantly higher than the dose used in the two previous investigations 300 mg vs 150 mg. This dose was selected according to the large volume of distribution of amiodarone and the expected hemodilution in the CPB reservoir. Even with this larger dose, it was unable to replicate the decrease in VF found by Samantaray and colleagues. **(Samantaray et al., 2010)**

Our results were similar to those of Ayoub and colleagues, who found no difference in the incidence of VF, but that VF was more easily terminated in patients receiving amiodarone. 29 patients who were taking amiodarone preoperatively had a decreased incidence of VF but not statistically significant and required fewer shocks to terminate VF but they suggest that an intravenous bolus of 300 mg of amiodarone may not be adequate to achieve therapeutic tissue levels in the myocardium. Future studies aimed at preventing reperfusion VF may focus on preoperative loading of patients with oral amiodarone.

Study Limitations

The current trial has some limitations. Despite enrolling a homogeneous surgical population. As noted earlier, the dose of administered amiodarone may not have been high enough to achieve therapeutic tissue levels given the added circulatory volume of the CPB circuit.

Conclusions:-

When applied to patients undergoing aortic valve surgical procedures, neither 300 mg of amiodarone nor 1.5 mg/kg of lidocaine with 2 g of magnesium sulfate administered 3 minutes before aortic cross clamp removal decreases the incidence of VF. However, amiodarone, but not lidocaine, reduces the number of shocks required to terminate VF after aortic cross clamp removal.

Conflict of interest

None

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