International Journal of

Innovative Drug Discovery

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

www.ijidd.com

Emergency Medicine

EFFECT OF INSULIN EUGLYCEMIC THERAPY IN NON-ISCHEMIC CARDIOGENIC SHOCK

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ABSTRACT

By increasing the catecholamine release, insulin has the ability to improve the cardiovascular functioning with limited evidences. Some studies also reported that myocardial function has improved followed by insulin administration without any increase in catecholamine levels. In 1999 on a report of drug-induced cardiogenic shock, with various drugs like amlodipine, atenolol and/or verapamil overdose, among 4 patient, no traditional therapy of antidote was proven to be effective in comparison with insulin-euglycemia therapy. Thus, reporting insulin euglycemic therepy (IET) to be more effective in improving cardiovascular functioning during drug-induced cardiogenic shock ,in similar way in septic 'cardiomyopathy' , heart failure with reduced ejection fraction (HFREF) which should be evaluated . Patients brought to the hospital with symptoms of cardiogenic shock which includes breathlessness, rapid heartbeat, low blood pressures, diaphoresis, low cardiac output, with adequate intravascular volume. The patients have cool and clammy extremities, poor capillary refill, tachycardia, narrow pulse pressure, and low urine output and pale skin have been enrolled into the study . The common symptoms observed in the study population included increased heart rate, low blood pressure for both systolic and diastolic. Decreased myocardial contractility activity resulting in decreased oxygen supply to the heart which was reflected as decreased central venous oxygen saturation (Scvo2) levels. It was clearly observed and concluded from the study that serum Lactate (mmol/L) has been reported to be slightly increased in insulin euglycemic therapy whereas, more elevated in other group. Ejection fraction is effectively maintained in IET group when compared with OTM group. Similarly mean arterial blood pressure values were maintained effectively in Insulin-euglycemic therapy group in comparison with other group. Thus, it can be concluded that insulin euglycemic therapy may be effective in management of non – ischemic cardiogenic shock , by shifting energy substrate from free fatty acid to glucose metabolism in non-ischemic cardiogenic shock. The preponderance of evidence demonstrates that the positive inotropic effects of insulin occur because of metabolic support of the heart during hypodynamic shock.

KEY WORDS: Insulin-Euglycemic Therapy (IET), Cardiogenic Shock (CS), Mean Arterial Pressure (MAP), Non-Ischemic cardiogenic shock, septic 'cardiomyopathy', Heart failure with reduced ejection fraction.

INTRODUCTION

For better approach of insulin euglycemic therapy it is to be known that in conditions like cardiogenic shock associated with vasodilation , bradycardia and/or decreased contractility like toxicity of calcium channel blocker (CCB) and beta-adrenergic antagonist (BAA) are the main cause which impacts and causes beta-adrenergic blockade and calcium channel blockade[1,2]. By increasing the catecholamine release, insulin has the ability to improve the cardiovascular functioning with limited evidences[3]. Some studies also reported that cardiogenic function is improved followed by insulin administration without any increase in catecholamine levels[4].

Other acceptable theory of insulin supporting for improved cardiovascular function includes, enhanced carbohydrates utilization by myocardium followed by administration of insulin[5]. In 1999 on a report of drug-induced cardiogenic

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shock, with various drugs like amlodipine, atenolol and/or verapamil overdose, among 4 patients, no traditional therapy of antidote was proven to be effective in comparison with insulin-euglycemia therapy[6]. Thus, reporting insulin to be more effective in improving cardiovascular functioning during drug-induced cardiogenic shock[7].

Insulin therapy also increased lactate uptake, most likely by restoring pyruvate dehydrogenase activity. In this way, lactate serves as a carbohydrate energy source following conversion to pyruvate and ultimately acetyl-CoA, which can then enter the Krebs cycle.

There is also evidence that insulin may have an effect beyond enhanced carbohydrate usage via direct effects on calcium and, to a lesser extent, potassium and sodium ion homeostasis. It appears that insulin may increase available intracellular calcium by enhancing reverse mode sodium/calcium exchange, with a resultant increase in the sarcoplasmic reticulum (SR) calcium load, thus causing increased contractility [24].

AIMS & OBJECTIVES:

- To perform and retrieve the effectiveness of insulin-euglycemia therapy in non-ischemic cardiogenic shock like drug induced cardiogenic shock , septic ‘’cardiomyopathy’’, heart failure with reduced ejection fraction (HFREF) and report on the same.
- To provide evidence on use of insulin-euglycemia therapy for improving cardiogenic shock and provide base for therapeutic approach of the same.
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MATERIALS & METHODS:

Materials: All the materials required for the study has been collected form the study site on getting approval from the heads of respective department and on singing of informed consent by the patients enrolled into the study.

Study type: Prospective observational study.

Study site: Kamineni institute of medical sciences, Narketpally, Nalgonda, Telangana state, India.
Study department: Department of Emergency Medicine , Kamineni Institute of Medical Sciences , Narketpally.

Ethical clearance: Study was carried out only after getting ethical clearance from the institutional ethics committee of the study site on brief submission of study protocol which included- methodology of the study, need and privacy retained data collection process.

Study population: Patients who have been admitted in the study site with a diagnosis of cardiogenic shock followed by any cause (drug induced, Septic ‘’cardiomyopathy’’, heart failure with reduced ejection fraction).
Study Duration: The study was carried in the supervision of experienced physicians, collecting all their guidance for a period of 12 months from Nov-2018 to Oct-2019.

Inclusion criteria: Patients brought to the hospital with symptoms of non-ischemic cardiogenic shock which included breathlessness, rapid heartbeat, low blood pressures, sweating, cold peripheries, low cardiac output, with adequate intravascular volume. The patients have cool and clammy extremities, poor capillary refill, tachycardia, narrow pulse pressure, and low urine output and pale skin [8-11].

Exclusion criteria: Age less than 12 and more than 70 years. Patients who are in their gestational period, patients with medical history of cardiovascular surgeries, unspecified drug allergies have been excluded from the study to maintain the consistency in the study report.

Statistical evaluation of the study:

Study reports have been statistically evaluated by using Super Anova statistical package, paired t-test for comparing the consistency between two different groups of the study and by performing ANOVA.

Parameters: Heart Rate (HR), Systolic Blood Pressure(SBP), Diastolic Blood Pressure(DBP), Mean Arterial Pressure (MAP), Central venous oxygen saturation (SCVO2), Serum Lactate, Ejection Fraction (EF) by 2D echocardiography.

RESULTS & DISCUSSION:

Insulin euglycemic therapy (IET) supports the metabolic demands associated with cardiogenic shock and augments calcium processing, thereby increasing myocardial contractility and improving tissue perfusion. Insulin mediated improved contractility appears to be a critical factor leading to survival from cardiogenic shock. In studies comparing insulin to more traditional therapies such as epinephrine and glucagon, insulin improves cardiac function and work efficiency (19).

All the patients who have been brought into the hospital with symptoms of non-ischemic cardiogenic shock have been approached and got enrolled into the study only after the acceptance of informed consent. The common symptoms observed in the study population included increased heart rate, low blood pressure for both systolic and diastolic. Decreased myocardial contractility activity resulting in decreased oxygen supply to the vital organs which was reflected as decreased central venous oxygen saturation levels (Scvo2) [12].

Table 1: Comparison of various parameters among the groups

Parameters	Insulin-Euglycemic therapy (IET)	Other therapeutic medication approaches (OMT)
HR (heart rate)	88 ± 6	105 ± 7
SBP (systolic blood pressure, mmHg)	112 ± 7	94 ± 3
DBP (diastolic blood pressure, mmHg)	86.2 ± 6.1	79 ± 5.4
MAP (mean arterial pressure, mmHg)	85 ± 10	84 ± 10
SCVO2 (central venous oxygen saturation) (%)	72 ± 3	66 ± 4
Serum Lactate (mmol/L)	2 ± 0.03	4 ± 0.01
Ejection fraction (2D - echo study) (%)	54	50

All the patients enrolled into the study have been divided into two groups. One group was given with Insulin-euglycemic therapy for treating non-ischemic cardiogenic shock and the other group has been treated with inotropic agents which are known to enhance the cardiovascular contractility which includes Dobutamine, Dopamine, Norepinephrine [13].

Various parameters that are known to be affected during non-ischemic cardiogenic shock has been observed which included Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Central venous oxygen saturation (SCVO2), Serum Lactate and Ejection Fraction (EF) using 2D- Echocardiography for assessment of left ventricular contractility [14].

As non-ischemic cardiogenic shock is a state of cardiac failure which results in end-organ hypoperfusion resulting in failure of cardiovascular system to supply adequate oxygen by pumping blood to the vital organs within the body[15]. Persistent hypotension with a systolic blood pressure of less than 80 to 90 mm Hg is frequently manifested to be persistent along with decrease in mean arterial pressure as less as 30 mm Hg which is considered as below baseline. Coming to the serum lactate levels, it was seen and evident that the serum lactate levels are slightly increased in all the cases of non-ischemic cardiogenic shock due to lack of myocardial efficacy to utilize glucose uptake[16]. Ejection fraction is considered usually for the left ventricle which is used as a measurement for percentage of blood leaving the heart on each time of contraction. During non-ischemic cardiogenic shock, ejection fraction is usually decreased to about 30% from the normal ejection fraction of above 55 %[17,18].

In the present study heart rate was observed to be 105 ± 7 mmHg in patients treated with other therapeutic medications (OTM) and it was 88 ± 7 in patients treated with insulin-Euglycemic therapy (IET). In IET , systolic blood pressure was assessed to be 112± 7 and 94 ± 3 mmHg in OTM group. Diastolic blood pressure was assessed to be 86.2 ± 6.1 in IET and 79 ± 5.4 in OTM group. Mean atrial pressure was reported to be 85 ± 10 in IET group and 84 ± 10 in OTM group. Central venous oxygen saturation was observed to be 72 ± 3 in IET and 66 ± 4 in OTM group. Serum lactate levels were recorded to be 2 ± 0.03 in IET and 4 ± 0.01 in OTM group. Ejection fraction was evaluated using 2D-Echo and it was observed to be 54% in IET and 50% in OTM group.

ADVERSE EVENTS:

The major anticipated adverse event associated with the use of large amounts of insulin, especially in patients naïve to insulin, is hypoglycemia, defined as blood glucose less than 60 mg/dL (3.3 mmol/L) regardless of the presence or absence of symptoms.

Because of potential hypoglycemia, all patients received sufficient dextrose during insulin infusion to maintain euglycemia. patients typically received empiric supplemental dextrose based on frequent glucose monitoring. The typical dextrose dose was 25 grams/hour, but requirements varied widely from 0.5 to 75 g/h. (20). The blood glucose should be monitored every 15 to 30 minutes until stable, and then every 1 to 2 hours. The dextrose infusion should be increased to maintain blood glucose concentrations between 100 and 250 mg/dL (5.5–14 mmol/L) rather than reducing the insulin.

Another anticipated consequence of insulin treatment is hypokalemia. Although serum potassium concentrations may fall below normal laboratory ranges, IET does not typically cause profound hypokalemia. The observed decrease reflects a shifting of potassium from the extracellular to intracellular space that occurs as a result of the action of insulin. Patients maintain normal total body potassium stores and do not experience true deficiency unless they have other reasons for potassium loss. In the initial case series, three patients had a nadir of potassium ranging from 2.2 to 2.8 mEq/L without sequelae (21).

DOSING:

Insulin therapy can be used by first administering a 1 unit/kg bolus of regular human insulin along with 0.5 g/kg bolus of dextrose. If blood glucose is greater than 300

mg/dL (16.7 mmol/L), then the dextrose bolus is not necessary. An infusion of regular insulin should immediately follow the bolus starting at 1 unit/kg/h,with frequent blood glucose monitoring.

Dosage titrated based on response, hemodynamics, hypoglycemic episodes. Further studies are necessary to determine bolus and infusion dosage [22,23].

CONCLUSION

It was clearly observed and concluded from the study that serum Lactate (mmol/L) has been reported to be slightly increased in insulin euglycemic therapy (IET) whereas, more elevated in OTM group. Ejection fraction is effectively maintained in IET group when compared with OTM group. Similarly central venous oxygen saturation (Scvo2) and mean arterial blood pressure (MAP) values were maintained effectively in Insulin-euglycemic therapy (IET) group in comparison with other group. Thus, it can be concluded that insulin can be recommended in addition to the standard treatment in non- ischemic cardiogenic shock . Further large trails are required to validate effectiveness of Insulin Euglycemic Therapy (IET), as few clinical trails are done earlier in respect to septic cardiomyopathy, heart failure with reduced ejection fraction . In particular, studying the dose - response relationship for loading dose and infusion are important, while reporting on presence of adverse effects.

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