Original Research Article

Effect of Mild Hypothermia on Morbidity and Mortality in Post AMI Cardiogenic Shock

Abstract

Background: Cardiogenic shock complicating acute myocardial infarction (AMI) is still associated with high mortality. Except for the proven benefit of early revascularization, other therapies such as intra-aortic balloon counter pulsation or medical therapy failed to improve prognosis in large-scale randomized trials. Recently, mild therapeutic hypothermia in which patients were cooled for 24 hours to 33°C has been discussed as a treatment option for patients in cardiogenic shock. The study is to assess the effect of mild hypothermia on morbidity and mortality of post AMI cardiogenic shock.

Methods: This randomized, controlled, unblinded trial was conducted on 50 patients with AMI complicated by CS. Patients were randomly allocated into two equal groups; group I received MTH to 33°C for 24-36 h and group II (control group) did not receive MTH. Patients were subjected to full history taking, general and clinical examination, laboratory examination, echo, chest ultrasound (US), coronary angiography data and mild therapeutic hypothermia protocol.

Results: Stroke until day 30, duration of mechanical ventilation, length of ICU stay, duration of inotropic support, mortality and pulmonary congestion by US were insignificantly different between both groups. Arterial lactate and mean arterial blood pressure (MAP) at 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h were significantly increased in group I than Group II (P value<0.05). and were insignificantly different between both groups at 0h, 2h, 22h, 24h, 26h,

28h, 30h. Serum creatinine at 24h, 48h was significantly increased in group I than Group II (p value <0.05) and was insignificantly different between both groups at 0h.

Conclusions: Therapeutic hypothermia (TH) didn't improve short term outcomes in patients with post AMI cardiogenic shock.

Keywords: Mild Hypothermia, Morbidity, Mortality, Post AMI, Cardiogenic Shock.

Introduction:

Cardiogenic shock complicating acute myocardial infarction (AMI) is still associated with high mortality. Except for the proven benefit of early revascularization, other therapies such as intra-aortic balloon counter pulsation or medical therapy failed to improve prognosis in large-scale randomized trials. Recently, mild therapeutic hypothermia in which patients were cooled for 24 hours to 33°C has been discussed as a treatment option for patients in cardiogenic shock [1].

A possible hemodynamic benefit of mild therapeutic hypothermia in cardiogenic shock may be an increase in myocardial contractility, cardiac output, and stroke volume [2].

Possible effects of mild therapeutic hypothermia on the heart in cardiogenic shock include a reduction in the overall metabolic rate, a reduction of the myocardial metabolic rate influencing reperfusion injury positively, and an increased cardiac contractility without an increase of oxygen consumption [3].

We therefore conducted a randomized small trial in patients with cardiogenic shock complicating AMI without classic indications for mild therapeutic hypothermia to investigate the hemodynamic effects of mild therapeutic hypothermia versus control on need for vasopressors and inotropes, serum lactate level and acute kidney injury.

Patients and Methods:

This randomized, controlled, unblinded trial was conducted on 50 patients with AMI complicated by CS at the department of cardiology, Aswan Heart Centre over a period of one year from October 2020 to September 2021 after being approved from the institution of ethical committee Tanta university. Written informed consent was obtained from all patients' guardian.

The inclusion criteria: Cardiogenic shock post AMI defined by systolic blood pressure <90 mm Hg for >30 minutes or motropes required to maintain a systolic blood pressure >90

mm Hg in the absence of hypovolemia with signs of pulmonary congestion and signs of impaired organ perfusion defined by at least 1 of the following: altered mental status; cold, clammy skin; urine output <30 mL/h; or arterial lactate >2 mmol/L and intubated and sedated.

The exclusion criteria: Self-ventilated, Indication for targeted temperature management by current guidelines "out of hospital cardiac arrest with ROSC and without neurological recovery.

The patients were randomly classified into two groups; 25 patients in each group. Randomization had been done by computer generated random numbers. The random number was placed in an opaque envelope.

Patients were assigned to: Group I received MTH to 33°C for 24-36 h and group II (control group): did not receive MTH.

All patients in this study were subjected to the following: History taking (personal history, risk factors as hypertension, diabetes mellitus, obesity, drug intake, smoking, prior stroke, prior myocardial infarction, prior PCI and comorbid diseases including renal, diseases or collagenic disorders), General examination, clinical examination (Vital signs as heart rate, blood pressure and respiratory rate), local cardiac examination (abnormal pulsation, Heart sounds and murmurs), Echo: All studies were performed using (a GE vivid 7 Dimension Cardiac ultrasound phased array system) equipped with a 2.5 MHz variable frequency transducer. Standard views according to American Society of Echocardiography. It was used to assess the structure heart disease, presence of resting segmental wall motion and assessment of the ejection fraction. Mechanical complication as ventricular septal rupture (VSR) and acute mitral regurgitation (AMR) and Chest U/S: pulmonary congestion by Ultrasound (US) was assessed.

Laboratory investigation: Arterial lactate, serum creatinine, mean arterial blood pressure, and norepinephrine and dobutamine dose were assessed at 0h, 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h, 22h, 24h, 26h, 28h, 30h, ALT and AST at 0h, 24h, 48h were assessed.

Coronary angiography data: Type of MI, Extent, left main stenosis, drug eluting stent (DES) used, TIMI flow before PCI, TIMI flow after PCI, ECMO, intra-aortic, sepsis and pneumonia were assessed for both groups. Outcome represented in stroke until day 30, duration of mechanical ventilation and Catecholamine support, length of Intensive care unit (ICU) stay, mortality. By comparing morbidity and mortality in both groups, morbidity (duration of mechanical ventilation, length of ICU stay and duration of inotropic support) and mortality were insignificantly different between the two groups.

Mild therapeutic hypothermia protocol: After PCI and transportation to the intensive care unit, cooling was maintained with a commercially available system (CoolGard, ZOLL Medical Corp) in patients receiving MTH (group I). By protocol, cooling down to the target temperature of 33°C was set at the maximum possible cooling rate. After the target temperature was reached, it was maintained for 24 hours with the automatic temperature regulation function of the CoolGard system by central temperature measurement in the urinary bladder. After 24 hours, rewarming was initiated with a speed of 0.25°C/h to a target temperature of 37.0°C. To avoid shivering in the MTH group, the patients were treated with a protocol including deep sedation and optional muscle relaxation. In patients randomized to control, no specific temperature control was applied.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were

presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. P value < 0.05 was considered statistically significant.

Results:

Patient's characteristics (age, sex and BMI) were insignificantly different between both groups. Hypertension (HTN), Hypercholesterolemia, Smoking, Prior stroke, Prior myocardial infarction, Prior myocardial infarction and Prior PCI were insignificantly different between both groups, however group I included more diabetic patients than Group II (P value <0.05). **[Table 1]**

Table 1: Patient's characteristics between both groups

	Group I (N = 25)	**Group II (N = 25)**	**P value**
Age (years)	61.4 ± 5.27	59.72 ± 5.82	0.290
	52 – 70	50 - 69	
Gender	19 (76.0%)	17 (68.0%)	0.529
	6 (24.0%)	8 (32.0%)	
BMI (kg/m^2)	30.93 ± 3.81	29.32 ± 3.72	0.139
	24.3 - 39.4	24.2 - 36.9	
HTN	21 (84.0%)	22 (88.0%)	0.684
DM	18 (72.0%)	9 (36%)	**0.022***
Hypercholesterolemia	14 (56.0%)	15 (60.0%)	0.775
Smoking	13 (52.0%)	11 (44.0%)	0.571
Prior stroke	6 (24.0%)	4 (16.0%)	0.480
Prior myocardial infarction	7 (28.0%)	9 (36.0%)	0.544
Prior PCI	6 (24.0%)	7 (28.0%)	0.747

BMI: body mass index. *Statistically significant as p value<0.05, HTN: hypertension, DM: diabetes mellitus, PCI: percutaneous coronary intervention.

Type of MI, extent, left main stenosis, DES used, TIMI flow before PCI, TIMI flow after PCI, ECMO, intra-aortic balloon pumb counter pulsation, sepsis and pneumonia) were insignificantly different between both groups. **[Table 2]**

Table 2: Type of MI, Extent, left main stenosis, DES used, TIMI flow before PCI, TIMI flow after PCI, ECMO, Intra-aortic balloon pumb counter pulsation, Sepsis and Pneumonia between both groups

		Group I (N = 25)	Group II (N = 25)	P value
Type of MI	**STEMI**	15 (60.0%)	17 (68.0%)	0.556

	Non-STEMI	10 (40.0%)	8 (32.0%)	
Extent	**1 Vessel**	6 (24.0%)	3 (12.0%)	0.397
	2 Vessel	8 (32.0%)	12 (48.0%)	
	3 Vessel	11 (44.0%)	10 (40.0%)	
Left main stenosis	**Present**	6 (24.0%)	4 (16.0%)	0.725
	Not present	19 (76.0%)	21 (84.0%)	
DES used	**Used**	19 (76.0%)	21 (84.0%)	0.725
	Not used	6 (24.0%)	4 (16.0%)	
TIMI flow before PCI = 0		7 (28.0%)	9 (36.0%)	0.544
TIMI flow after PCI = 3		20 (80%)	21 (84.0%)	0.952
ECMO	**Used**	2 (8.0%)	3 (12.0%)	0.667
	Not used	23 (92.0%)	22 (88.0%)	
Intra-aortic balloon pumb counter pulsation	**Used**	13 (52.0%)	16 (64.0%)	0.390
	Not used	12 (48.0%)	9 (36.0%)	
Sepsis	**Developed**	3 (12.0%)	1 (4.0%)	0.334
	Not Developed	22 (88.0%)	24 (96.0%)	
Pneumonia	**Developed**	9 (36.0%)	11 (44.0%)	0.564
	Not Developed	16 (64.0%)	14 (56.0%)	

MI: acute myocardial infarction, DES: Drug eluting stent, TIMI: Thrombolysis in Myocardial Infarction, ECMO: extracorporeal membrane oxygenation.

Total leucocytic count and Baseline serum creatinine were insignificantly different between both groups before intervention. Heart rate, systolic blood pressure, diastolic blood pressure and EF were insignificantly different between both groups. **[Table 3]**

Table 3: Total leucocytic count, baseline serum creatinine, heart rate, systolic blood pressure, diastolic blood pressure and EF between both groups before intervention

	Group I (N = 25)	Group II (N = 25)	P value
Total leucocytic count (*10^3 cells/dl)	12.60 ± 1.89	12.89 ± 2.27	0.628
	9 - 15.8	9.3 - 16.8	
Baseline serum creatinine (mg/dL)	2.28 ± 0.39	2.17 ± 0.39	0.314
	1.5 - 2.8	1.5 - 2.8	
Heart rate (beats/min)	83.40 ± 22.80	85.92 ± 16.34	0.655
	51 – 120	50 – 117	
Systolic blood pressure (mmHg)	82.80 ± 8.08	86.08 ± 9.08	0.184
	71 – 96	70 – 100	
Diastolic blood pressure (mmHg)	54.24 ± 9.22	57.88 ± 10.73	0.204
	41 – 73	41 – 76	
EF (%)	31.68 ± 4.71	32.44 ± 5.12	0.587
	25 – 39	25 – 40	

BMI: body mass index, EF: ejection fraction.

Stroke until day 30, duration of mechanical ventilation, length of ICU stay, duration of inotropic support, mortality and pulmonary congestion by US were insignificantly different between both groups. **[Table 4]**

Table 4: Outcome between both groups

		Group I (N = 25)	Group II (N = 25)	P value
Stroke until day 30		0 (0.0%)	2 (8.0%)	0.490
Duration of mechanical ventilation (days)	**Mean ± SD**	4.88 ± 2.44	5.40 ± 2.22	0.434
	Range	2 – 10	2 – 10	
Length of ICU stay (days)	**Mean ± SD**	6.76 ± 3.13	7.08 ± 2.83	0.706
	Range	2 – 11	2 – 12	
Duration of inotropic support (days)	**Mean ± SD**	3.92 ± 2.55	4.72 ± 2.15	0.236
	Range	1 – 10	2 – 10	
Mortality	**Died**	13 (52.0%)	16 (64.0%)	0.390
	Survived	12 (48.0%)	9 (36.0%)	
Pulmonary congestion by US (3 B lines or more)		18 (72.0%)	16 (64.0%)	0.544

US: ultrasound

Arterial lactate at 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h was significantly higher in group I than Group II (P value <0.05). and was insignificantly different between both groups at 0h, 2h, 22h, 24h, 26h, 28h, 30h. **[Figure 1]**

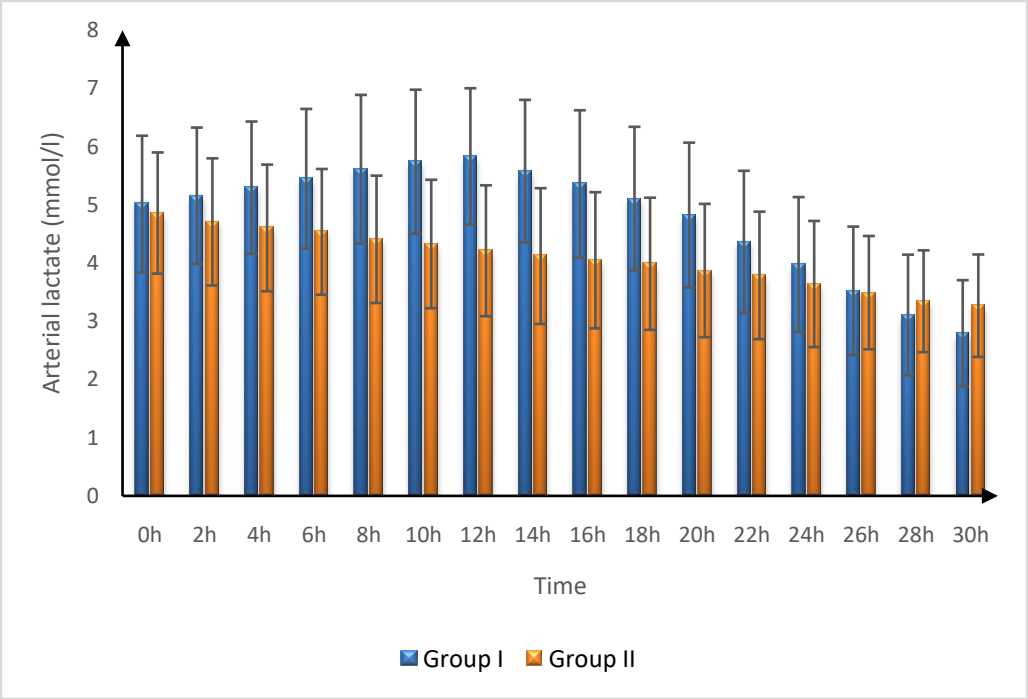


Figure 1: Arterial lactate in both groups

MAP at 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h was significantly higher in group I than Group II (P value <0.05). and was insignificantly different between both groups at 0h, 22h, 24h, 26h, 28h, 30h. **[Figure 2]**

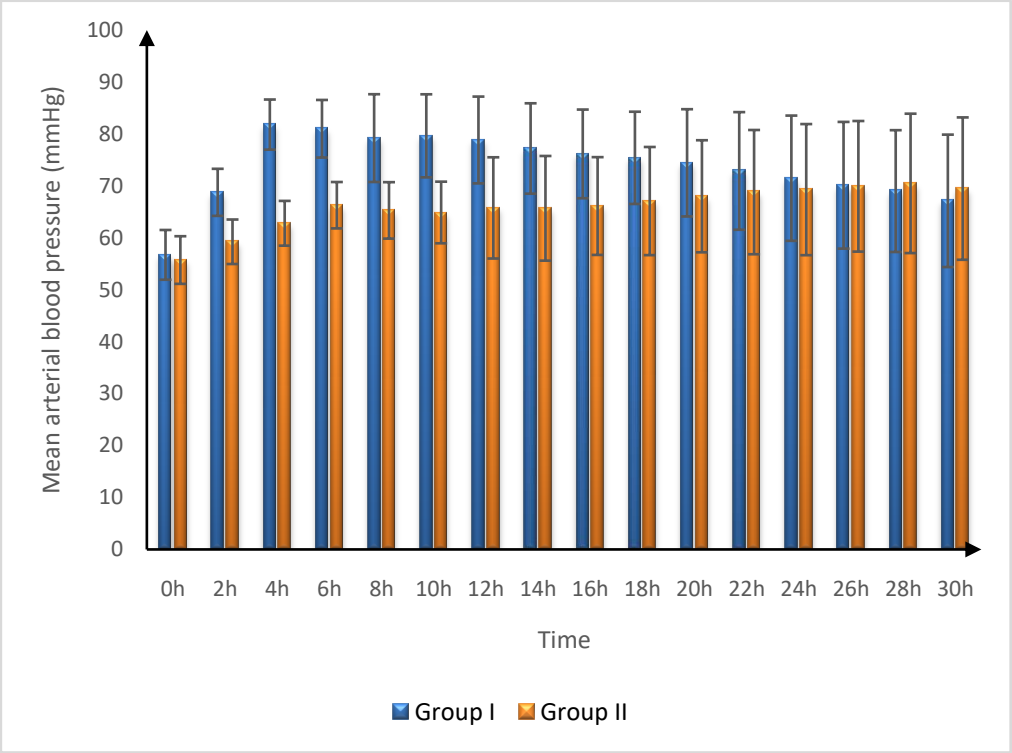
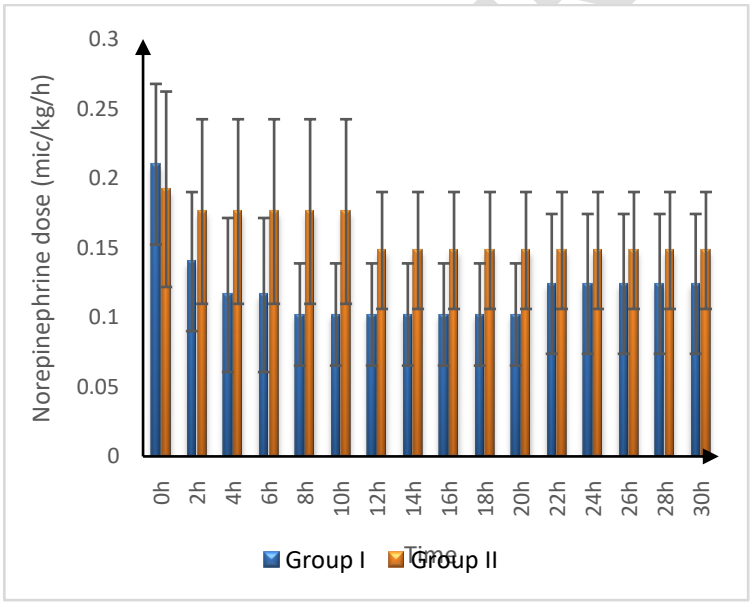
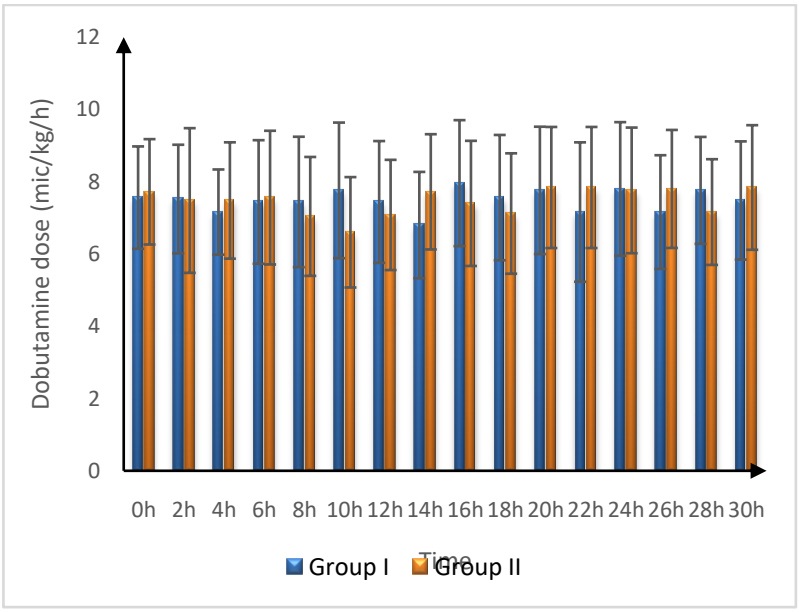


Figure 2: Mean arterial blood pressure in both groups

NE at 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h was significantly decreased in group I than Group II (P value <0.05). and was insignificantly different between both groups at 0h, 22h, 24h, 26h, 28h, 30h. Dobutamine dose at 10h was significantly increased in group I than Group II, was significantly decreased in group I than Group II at 14h (P value <0.05) and was insignificantly different between both groups at 0h, 2h, 4h, 6h, 8h, 12h, 16h, 18h, 20h, 22h, 24h, 26h, 28h, 30h. **[Figure 3]**



(A)



(B)

Figure 3: Doses of (A) NE (mic/kg/h) and (B) Dobutamine (mic/kg/h) between both groups

ALT and AST at 0h, 24h, 48h were insignificantly different between both groups. Serum creatinine at 24h, 48h was significantly increased in group I than Group II (p value <0.05) and was insignificantly different between both groups at 0h. **[Table 5]**

Table 5: ALT, AST and serum creatinine between both groups

		Group I (N = 25)		Group II (N = 25)		P value
		Mean	**± SD**	**Mean**	**± SD**	
ALT	0h	292.20	66.35	309.24	66.42	0.369
	24h	283.72	57.37	281.32	61.47	0.887
	48h	298.80	60.48	291.88	57.12	0.679
AST	0h	290.04	54.18	298.32	54.90	0.594
	24h	316.60	59.12	306.20	50.45	0.507
	48h	313.68	67.81	298.40	64.68	0.419
Serum creatinine	0h	2.28	0.39	2.17	0.39	0.314
	24h	2.37	0.43	1.94	0.37	**<0.001***
	48h	2.25	0.46	1.85	0.39	**0.002***

ALT: alanine aminotransferase, AST: aspartate aminotransferase, *Statistically significant as p value<0.05.

Discussion

Cardiogenic shock affects approximately 7%–9% of all patients with acute myocardial infarction (MI) and continues to be the major cause of mortality in patients hospitalized with acute MI. Despite optimal medical therapy, urgent revascularization, and advances in mechanical support, mortality of post-MI cardiogenic shock continues to exceed 40%. Unfortunately, despite this considerable mortality rate, few recent advances have been made in the management of cardiogenic shock, and investigation into alternative therapeutic options is needed [4].

In the present study, prior stroke, prior myocardial infarction, and prior PCI were insignificantly different between both groups, except DM that was significantly increased in group I than Group II. Conforming to our results, **Fuernau et al.**[5] found that prior stroke, prior myocardial infarction, and prior PCI were insignificantly different MTH treated and control group.

Our study found that type of MI, extent, left main stenosis, DES used, TIMI flow before PCI, TIMI flow after PCI, ECMO, intra-aortic, sepsis and pneumonia were insignificantly different between both groups. Heart rate, systolic blood pressure, diastolic

blood pressure and EF were insignificantly different between both groups. The results of our analysis are in line with **Fuernau et al.**[5] who declared that left main stenosis, TIMI flow before PCI, TIMI flow after PCI, intra-aortic, and pneumonia showed no significant difference between MTH and the control group.

In the present study, heart rate, systolic blood pressure, diastolic blood pressure and EF were insignificantly different between both groups. However, **Zobel et al.**[6] studied the hemodynamic effects of mild therapeutic hypothermia in 20 consecutive patients admitted in cardiogenic shock after successful resuscitation from out-of-hospital cardiac arrest were investigated. A historic normothermic control group was matched (one-to-one) by means of a propensity score. Patients were cooled to 33°C for 24 hrs using an endovascular cooling device and hemodynamic variables were continuously recorded by means of pulse contour analysis. Cardiac performance was determined by echocardiography, reported that mild therapeutic hypothermia induced a significant decrease in heart rate from 74 to 64 beats per minute ($p < .05$). Moreover, the study noted an increase in ejection fraction from 43 ± 4% to 55± 4%. The small sample size that was included may account for this contradiction. Similar to our findings, **Fuernau et al.**[5] observed no relevant differences between MTH and the control group in terms of systolic blood pressure, and diastolic blood pressure.

In our study, stroke until day 30, duration of mechanical ventilation, length of ICU stay, duration of catecholamine support and mortality were insignificantly different between both groups. Conforming to our results, **Annborn et al.** [7] reported that (ICU) and 30-day mortality had no significance difference between targeted temperature management at 33°C or 36°C. In contrast, **Zobel et al.**[6] documented that catecholamine use was significantly lower in patients with cardiogenic shock subjected to hypothermia; the small sample size that was included may account for this contradiction.

In the present study, arterial lactate at 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h was significantly increased in group I than Group II (P value<0.05). and was insignificantly different between both groups at 0h, 2h, 22h, 24h, 26h, 28h, 30h. In contrast, **Fuernau et al.**[5] results declared that arterial lactate decreased over time in both groups with a slower and flatter decrease in the MTH group. The large used sample size may clarify this difference.

In our study, MAP at 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h was significantly increased in group I than Group II (P value <0.05) and was insignificantly different between both groups at 0h, 22h, 24h, 26h, 28h, 30h. As opposed to our results, **Young et al.**[8]

included 188 consecutive patients following cardiac arrest that had successful ROSC and were treated with TH at Vanderbilt University Medical Center between May 2007 and March 2012. All patients were cooled externally using an active surface-cooling device to maintain a core body temperature of 32–34 degrees Celsius for a total of 24 hours following ROSC, after which they were rewarmed actively at a rate of 0.25 degrees Celsius per hour. The standardized TH protocol at our institution recommends a MAP target of 80–90 mmHg and norepinephrine as the initial vasopressor of choice to treat hypotension. The study found that patients achieved similar MAP before and during TH (80.3 versus 83.7 mmHg; p=0.11). This difference may be linked to the larger used sample size and the study design. In contrast to our results, **Fuernau et al.**[5] observed no differences in MAP between MTH treated group and the control group. This difference could be justified by the large, recruited sample size.

In our study, NE at 2h, 4h, 6h, 8h, 10h, 12h, 14h, 16h, 18h, 20h was significantly decreased in group I than Group II (P value <0.05) and was insignificantly different between both groups at 0h, 22h, 24h, 26h, 28h, 30h. Also, **Zobel et al.**[6] reported that under normothermic treatment almost all patients (80%) required increasing doses of norepinephrine and for that the control group, rate of infusion of norepinephrine could be reduced significantly upon induction of hypothermia.

In our present study, Dobutamine dose at 10h was significantly increased in group I than Group II, was significantly decreased in group I than Group II at 14h (P value <0.05) and was insignificantly different between both groups at 0h, 2h, 4h, 6h, 8h, 12h, 16h, 18h, 20h, 22h, 24h, 26h, 28h, 30h. Comparable to our results, **Fuernau et al.**[5] highlighted that dobutamine had a faster decline in the MTH group than the control group. Our results were consistent with **Jacobshagen et al.** [9]study**.** In the study they investigated the influence of therapeutic hypothermia on hemodynamic parameters in resuscitated patients and on contractility in failing human myocardium. They analyzed hemodynamic data from 200 cardiac arrest survivors during the hypothermia period. The study found that the dobutamine application rates was not changed significantly before and after hypothermia (P = 0.23).

Serum creatinine at 24h, 48h was significantly increased in group I than Group II (p value <0.05) and was insignificantly different between both groups at 0h. In contrast to our results, **Fuernau et al.** [5] results showed serum creatine that did not differ between treatment groups (MTH versus control). Large, recruited sample size could justify this variance. However, **Stegman et al.** [10] after analyzing serial hemodynamics of 14 consecutive patients

with cardiogenic shock after cardiac arrest treated with TH, they declared that serum creatinine did not significantly change from baseline to 24 hours (1.52 ± 1.0 vs. 1.45 ± 0.6 mg/dl, p=0.63). The short follow up duration of the serum creatinine level could justify this opposition.

In our study, ALT at 0h, 24h, 48h was insignificantly different between both groups. AST at 0h, 24h, 48h was insignificantly different between both groups. In line with our results, **Mulalic et al.** recruited 101 patients diagnosed with acute stroke were treated. The first group (n=40) were treated with conventional treatment and therapeutic hypothermia, while the second group (n=61) only with conventional treatment. Cooling of the body to a target body temperature of 34°C to 35°C was performed for up to 24 hours. Outcome (survival or death) of treatment was monitored, degree of disability was determined by National Institutes of Health Stroke Scale (NIHSS) and assessment of consciousness using the Glasgow Coma Scale (GCS). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were taken at admission, after 24 hours, and were monitored upon discharge. They found that although patients treated with therapeutic hypothermia recorded decreased mean AST values after 24 hours (32.50 to 31.00 IU/mL) as well as ALT values (27.50 to 26.50 IU/mL), the difference was not statistically significant.

Conclusions:

Therapeutic hypothermia (TH) didn't improve short term outcomes in patients with post AMI cardiogenic shock.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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