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Effects of Therapeutic Hypothermia on Improving Neurological Recovery and Reduction of Mortality After Global Ischemia in Patients with Myocardial Infarction

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Abstract

Background: An estimate of 5 million patients is admitted to the ER in US per annum with the chief complaint of acute chest pain and over 800,000 people have an acute myocardial infarction (AMI) of which 27% pass away, most of them before even reaching the hospital. The aim of the article is to review better methods that can be provided to such patients so that it may increase their likelihood of short as well as long-term survival, especially evaluate if hypothermia improves the neurological recovery and reduces mortality after a global ischemia in patients with Myocardial Infarction.

Methods: By using "Hypothermia in patients with myocardial infarction, therapeutic hypothermia, hypothermia therapy for patients with MI" we search articles in MEDLINE, COHRANE, The Lancet, The New England Journal of Medicine with restricted data from 2013-2022. For selection criteria of the articles were English language, types of study, such as Research articles, review articles, case reports, clinical trials and case studies were used. For review we choose only articles with full text available.

Results: A total of seven research papers were selected for the study, encompassing a diverse patient population of 1,066 individuals with a history or current presence of myocardial infarction (MI). The sample was comprised of individuals from various ethnic and socio demographic backgrounds.

Conclusions: The objective of the review was to evaluate the evidence supporting the hypothesis that administering hypothermia therapy to patient's post-myocardial infarction (MI) can improve short- and long-term outcomes, compared to not receiving the therapy. A range of methods were utilized to achieve hypothermia, with a target temperature of 31-34°C.

The results of the included studies indicated that the administration of therapeutic hypothermia was associated with improved outcomes, including improved cardiac rhythm, better neurological function, reduced mortality rates, and a significantly higher number of patients alive at hospital discharge, compared to the control group not receiving therapeutic hypothermia.

INTRODUCTION

An estimated 5 million patients visit the ER in US per annum with the chief complaint of acute chest pain and over 800,000 people have an acute myocardial infarction (AMI) of which 27% pass away, most of them before even reaching the hospital.[1] Myocardial Infarction (MI) may lead to compromised blood flow to a region of the heart leading to ischemia and tissue necrosis and the aim of contemporary therapy in patients with an ongoing ST-elevated MI is to restore blood flow to the ischemic muscles quickly and reduce to the possible Infarct Size (IS) and its associated complications, it is of importance to note that the IS is one of the main predictors of outcomes for a patients both in the long and short terms in patients who have had an AMI hence if the IS is reduced it can lead to better outcomes and a better prognosis of patients with AMI.[2]

It is of paramount importance to restore the blood flow to the myocardium in order to salvage the muscle although it may cause irreversible damage to the myocardium which is known as "reperfusion injury" hence to reduce this reperfusion injury, which leads to a higher IS and a poorer short- and long-term prognosis, we employ the use of hypothermia in parallel to the traditional therapies.[3]

Therapeutic hypothermia as a method for the treatment of MI

Therapeutic hypothermia (TH) is the induction of hypothermia in order to limit organ damage after an ischemic episode. According to current evidence, TH can be a promising method to reduce post-Ischemia myocardial injuries.[4] The Physiology behind this is that TH protects the myocardial tissue mostly through reducing oxygen demand of the heart by causing bradycardia which leads to limitation of the subsequent damage. Also, upon reperfusion, through influencing multiple pathways, less reactive oxygen species are released which limits reperfusion injury.[5] Hypothermia has several levels including mild [32-35 C], moderate [28-32 C], severe [20-28 C], and profound [<20 C].[4]

Hypothermia is mainly achieved through two general methods; the more conventional technique is surface cooling which has been practiced for many years in different situations. In this method the time needed for reaching the target temperature strictly depends on the patient's body surface area. In surface cooling technique ice packing, water mattresses, and etc. are used. External cooling takes time and has concerning physiological disadvantages for the individual including shivering which results in counteraction of the heat produced due to continuous muscle contraction.[6] The second method is known as endovascular cooling and has come into practice in recent years which uses heat-exchange catheters. Although its performance requires fully trained and professional health care staff, it is more convenient than surface cooling in many ways. Another way of achieving target low temperature internally is through infusion of cold fluids.[2]

In more recent literature, methods for achieving therapeutic hypothermia are divided into systemic and selective.[7] Systemic involves generalized decrease in body temperature by either surface cooling or low temper IV saline infusion and it is followed by shivering thus uncomfortable for the patient. Another downside to systemic hypothermia induction is that it takes a relatively long time (1-7.36 h) to reach the targeted temperature which results in missing the optimal time window for the treatment. On the other hand, it can only have an Inter-reperfusion/postreperfusion onset because it requires a completely different procedure than reperfusion therapy and has to be delayed until after. Which means it would not be much helpful with alleviating the reperfusion injury in an emergency setting.

The selective method is quicker to achieve and gives us the benefit of inter-ischemic/pre perfusion onset which is beneficial to prevent the reperfusion injury to a great extent. In this method, only the area of interest is cooled down which omits shivering and patient discomfort. Intra-arterial- selective cooling infusion (IA-SCI) is the most studied type of selective hypothermia induction and has been shown to have promising results if initiated less than 6 hours after the ischemic episode. Despite the good result, IA-SCI preformation is only possible on PCI candidates.[8]

TH has shown to be useful in preventing large infarct areas post MI due to ischemia and also, reperfusion injury in out-of-hospital cardiac arrest (OHCA) situations. For achieving satisfying results, TH has to be initiated immediately after resuscitation and it should continue throughout the cardiac catheterization procedure. Performing TH in OHCA has been associated with remarkable improvements in ischemic areas and infarct sizes.[9]

According to a systemic review done by Karcioglu et al., despite the possibility of adverse side effects, practice of TH in the event of cardiac ischemia is considered fairly safe. Also, surface cooling method in comparison with endovascular method showed no different complications.[9]

To come to the adverse effects of hypothermia, induced hypothermia carries the risk of a few adverse effects in general. Cardiac arrhythmia, increase risk of coronary artery constriction, systolic and diastolic dysfunction which can lead to decreased contractility of myocardium are some of the presumed adverse effects on the heart. In addition to this, electrolyte imbalance is also seen. Low temperature leads to increased renal excretion of multiple electrolytes such as magnesium, potassium, calcium, and phosphorus. In the situation of hypothermia, insulin secretion and sensitivity drop, leaving the patient in a hyperglycemic state.[10]

METHODOLOGY

We conducted a comprehensive literature search focusing on the role of hypothermia in patients with myocardial infarction, utilizing specific search terms including “Hypothermia in patients with myocardial infarction,” “therapeutic hypothermia,” and “hypothermia therapy for patients with MI.” The search was carried out across reputable databases, including MEDLINE, COCHRANE, The Lancet, and The New England Journal of Medicine, covering the period from 2013 to 2022.

Search Terms:

- "Hypothermia in patients with myocardial infarction"
- "Therapeutic hypothermia"
- "Hypothermia therapy for patients with MI"
-

Databases:

- MEDLINE
- COCHRANE
- The Lancet
- The New England Journal of Medicine

Inclusion Criteria: To ensure the relevance and quality of the selected articles, we applied the following criteria:

1. Language: Articles were included if published in the English language.
2. Study Types: Various types of studies were considered, including research articles, review articles, case reports, clinical trials, and case studies.
3. Review Selection: For review articles, only those with full-text availability were chosen, ensuring a comprehensive and thorough examination of the selected literature.

This systematic approach allowed us to gather a robust and up-to-date collection of articles pertaining to the use of hypothermia in the context of myocardial infarction. The selected studies encompass a diverse range of study types to provide a comprehensive understanding of the therapeutic effects and outcomes associated with hypothermia therapy in patients with myocardial infarction.

RESULTS

In an experiment with a safe method in myocardial hypothermia (Table 1), in two types of patients with stable angina and ST-elevation myocardial infarction, which included intra coronary infusion of saline with sizes of 10 to 30 ml/Min and at room temperature, it was found that in all these patients, Intra-coronary hypothermia was achieved fast and without complications.[12]

Regarding timing and the importance of neurological outcomes, according to the studies in Table 2, analyzed 48 patients who underwent emergency coronary angiography for STEMI after witnessed OHCA, it was found that in both the mild hypothermia therapy (MTH) and control groups, a delay in hypothermia treatment of 30 seconds resulted in a 1-year mortality rate in the MTH group to be about 37% and in the control group to be 50%. So acceptable long-term neurological results were higher in the MTH group with intra-vascular cooling due to STEMI.[13] In the following, focusing on the obtained neural results, we can refer to another experiment in

Table 2, in which a study was conducted on 58 OHCA patients, in which 23 patients underwent TH by maintaining a temperature of 32 to 34 degrees Celsius for 24 hours. but 35 patients had standard care without TH. In this test, more than 50% of the patients in the TH group had favorable neurological results, but in the control group, this rate was only around 20%.[8]

483 consecutive patients treated with PCI for a first anterior STEMI, in relation to the mortality rate and the effect of this treatment method with a combination of angioplasty, in patients who suffered from blood flow disorders at the level of the heart myocardium, the proportion of those who before pre-percutaneous coronary intervention (PCI), have had, 38% to 75% compared to those who have not had hypothermia treatment (Table 4).

And in another observation of 26 people who died, the mortality rate was 46% to 83% in patients who received Therapeutic Hypothermia compared to those who did not receive Therapeutic Hypothermia.[14]
Following this result, we can refer to other similar findings in Table 5, the combination of MTH with primary PCI is very effective in the treatment of patients who had out-of-hospital cardiac arrest due to STEMI.[15]

In the meantime, referring to the neurological consequences in two observations, it can be noted that in Table 3, Four patients resuscitated from cardiac arrest were treated with mild hypothermia therapy for 24 to 40 hours.

During this time, they were monitored by neurologists and all 4 patients had a significant improvement after 24 hours after rewarming and were discharged without or with minimal complications.

All treatments in the hospital environment, for more control, should be considered in non trust mode for up to 72 hours, and different evaluations such as markers of brain damage or EEG and clinical examinations should be used for more control.[16]

And also, 367 patients with an average age of 60 years, it was found that more than 90% of them (99.7%) completed the test. They were divided into two groups with two different temperatures for treatment, and according to the results, it can be said that the temperature of 31 °C did not cause a significant change in the mortality rate or neurological results compared to the temperature of 34 °C.[17]

Table 1

Author (year)	Number	Cooling system	Mean time reaching target temperature
Luuk C Otterspoor, et al. (2015 Aug 13) (12)	53 patients with stable angina 20 patients with STEMI	continuous selective intra coronary infusion of saline (rates between 10 ml/Min and 30 ml/Min)	patients with stable angina: Ti was -5.65 ± 1.41°C Td was -0.78 ± 0.51°C patients with STEMI: Ti was -7.45 ± 0.51°C Td was -1.37 ± 0.82°C

Table 2

Author (year)	Number	Cooling System	Median time delay	Initial rhythm	alive at hospital discharge	One-year mortality	neurological outcome
Stefan Zimmermann MD, et al. (06 May 2013) (13)	48 patients	mild hypothermia therapy was performed via intra-vascular cooling (34°C for 24 hours) By rapid infusion of cold saline	6 minutes (MTH group) 6.5 minutes (controls) (P = 0.16)	75% vs 66.7% (P = 0.75)		37.5% (MTH group) vs 50% (controls) (P = 0.56)	58.3% vs 20.8%, P = 0.017)
Po-Yen Ko, et al. (2019 Jul; 35(4): 394–401.) (9)	58 OHCA patients	23 patients with TH, and 35 patients without TH	TH group: To maintain a body temperature of 32-34 °C for 24 hours and Control group received standard supportive care		(73.91% vs. 31.43%, p=0.0015)		52% (12 of 23) vs. 20% (7 of 35) (p = 0.01).

Table 3

Author (year)	Number	Cooling system	neurological outcome	Mortality	Thrombosis
Demetris Yannopoulos, et al. (2007 Nov) (16)	4 comatose patients	Mild hypothermia (32 °C - 33 °C) for 24 to 40 hours	neurology recovery 9 to 24 hours after rewarming to normothermia		
Michel Le May, et al. (2021 Oct 19) (17)	367 patients	- 89 of 184 patients (48.4%) in the 31 °C group - 83 of 183 patients (45.4%) in the 34 °C group	temperature of 31°C did not cause a significant change in the mortality rate or neurological results compared to the temperature of 34°C	Mortality in 180 days: 43.5% and 41.0% in patients treated with a target temperature of 31 °C and 34 °C, respectively (P = .63)	deep vein thrombosis: 11.4% vs 10.9% thrombus in the IVC: 3.8% and 7.7%,

Table 4

Author (year)	Number	Cooling system	outcome	in-hospital death
Makoto Suzuki, et al. (Volume 8, 1 September 2015, Pages 108-113) (14)	483 consecutive patients treated with PCI for a first anterior STEMI	13 patients were treated with pre-PCI procedural therapeutic hypothermia 24 were not inducted with therapeutic hypothermia	5 patients with and 18 without pre-PCI procedural therapeutic hypothermia impaired myocardial tissue level reperfusion (38% vs. 75% (p = 0.037)	70% (6 patients with and 20 patients without therapeutic hypothermia (in-hospital mortality 46% vs. 83% (p = 0.028))

Table 5

Author (year)	Number	Cooling System	mortality	neurological outcome
Wolfrum, Sebastian MD, et al. (June 2008 - Volume 36 - Issue 6 - p 1780-1786) (15)	33 patients after cardiac arrest with ventricular fibrillation and presented with acute ST elevation myocardial infarction (STEMI)	Target temperature (32– 34°C) in the MTH group (within 4 hours)	patients treated with MTH Have a lower mortality after 6 months (25% vs. 35% (p = .71)	(69% vs. 47% in the control group (p = .30)

DISCUSSION

In this article we discussed about the experimental adjunct treatment in which a patient with MI is induced with hypothermia by decreasing their body temperature by a few degrees (by either systemic or endovascular way) so that the reperfusion injury as well as ischemia can be minimized. The must consider the sensitivity of this protocol as there are many challenges that are faced by both the involved personnel; health care providers and the patient, the health care providers must take special care of a few key elements. firstly, to make sure that the hypothermia is induced as soon as possible after an MI episode, a new challenge arises in this aspect that the healthcare providers must be trained in the special techniques that will allow for them to carry out this procedure efficiently, secondly, the health care providers must make sure that the desired temperature is maintained and doesn't fluctuate too much which may cause more stress, for this special cooling blankets and equipment are available but the cost of these must be considered too.

finally, the health care providers must also be trained and a protocol must be put into place to follow if the patient becomes critical in this state or if the patient is not handling the induced hypothermia well. Moving on to the challenges that may be faced by the patient include the consideration that the being in a state of prolonged hypothermia has a physical and a mental toll as the patient is already under stress due to the MI, the hypothermia may add to it hence, measures should be taken to come to a middle ground where the treatment is not compromised and the stress levels of the patient are not high. This adjunct treatment option is still in need of further investigation with a more diverse as well as larger sample size and a decision to make this a part of the usual protocol of treatment of MI cannot yet be made subjectively but must be made based on the condition of the patient, the available resources and after the harm and benefits have been weighed.

CONCLUSION

According to the studies conducted, it can be noted that there is an acceptable outcome from these experiments in support of the hypothesis that induced TH can lead to reduced mortality and a better short- and long-term prognosis and that hypothermia should be done soon after an MI as a delay can have significant effects on mortality and adverse neurological outcomes. Timely hypothermia, particularly in the hospital setting, increases the percentage of positive neurological results to more than 50% and the chance of survival in the hospital to more than 70%.

These standard methods can be combined to include PCI with MTH as a standard treatment in the recovery of OHCA caused by STEMI or cold saline at room temperature with Endovascular Catheter Cooling in the treatment of myocardial infarction. [CHILL-MI].

DECLARATION

Ethical Statement

The research conducted in this study has received approval from the Institutional Review Board/Ethics Committee at Ivane Javakhishvili Tbilisi State University. All procedures performed in this study involving human participants were in accordance with the ethical standards of Ivane Javakhishvili Tbilisi State University and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

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Conflicts of Interest

The authors maintain that there are no conflicts of interest related to this research. Neither financial nor non-financial competing interests are present.

Data Availability

The data supporting the findings of this study are comprehensively presented within the article and its supplementary materials. For any additional data, interested parties may request access, and such requests will be considered.

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