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Research Article / Araştırma

The use of Therapeutic Hypothermia in Patients Having Cardiac Arrest

Kardiyak Arrest Gelişen Hastalarda Terapötik Hipotermi Uygulaması

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ABSTRACT

Objectives: Therapeutic hypothermia (TH) is applied to regain the quality of life in patients whose spontaneous blood circulation returns after cardiopulmonary resuscitation (CPR). In our study, we investigated the effects of TH after CPR.

Methods: The findings of patients who underwent TH (Group 1, n=32) were compared with those of normothermic patients (Group 2, n=37) in this retrospective study. Recorded data were demographic data, comorbid diseases, causes of cardiac arrest, cardiac arrest rhythms, return times of spontaneous circulation, Glasgow coma scale, deep tendon reflex and brainstem reflex, extubation times, durations of intensive care unit (ICU) stay, and complications.

Results: Extubation time in Group 1 (4.74±2.80 days) was shorter than in Group 2 (9.55±10.16 days). The length of stay in the ICU was shorter in Group 1 (7.96±5.10 days) compared to in Group 2 (13.40±11.40 days). Incidence of epileptic seizure activity was lower in Group 1 (16.2%) than in Group 2 (46.9%). Although Glasgow coma scale score evaluated at discharge was higher in Group 1, this difference was not statistically significant (p>0.05).

Conclusion: We consider that the use of TH in patients whose spontaneous blood circulation was restored by CPR procedure after cardiac arrest has significant and positive effects on recovering the quality of life.

Keywords: Cardiopulmonary resuscitation, normothermia, therapeutic hypothermia

ÖZ

Amaç: Kardiyopulmoner resüsitasyon sonrası spontan kan dolaşımı geri dönen hastalarda yaşam kalitesinin yeniden kazanılmasında terapötik hipotermi uygulanmaktadır. Çalışmamızda kardiyopulmoner resüsitasyon sonrası terapötik hipoterminin etkilerini araştırdık.

Yöntem: Bu retrospektif çalışmada terapötik hipotermi yapılan hastaların (Grup 1, n=32) bulguları normotermik hastaların (Grup 2, n=37) bulguları ile karşılaştırıldı. Kaydedilen veriler; demografik veriler, komorbid hastalıklar, kardiyak arrest nedenleri, kardiyak arrest ritimleri, spontan dolaşım dönüş süreleri, Glasgow koma skalası, derin tendon refleksi ve beyin sapı refleksi, ekstübasyon süreleri, yoğun bakımda kalış süreleri ve komplikasyonlardır.

Bulgular: Ekstübasyon süresi Grup 1'de (4,74±2,80 gün) Grup 2'den (9,55±10,16 gün) daha kısaydı. Yoğun bakımda kalış süresi Grup 1'de (7,96±5,10 gün) Grup 2'ye (13,40±11,40 gün) göre daha kısaydı. Epileptik nöbet aktivitesinin insidansı Grup 1'de (%16,2) Grup 2'ye (%46,9) göre daha düşüktü. Grup 1'de taburculukta değerlendirilen Glasgow koma skalası skoru daha yüksek olmasına rağmen bu fark istatistiksel olarak anlamlı değildi (p>0,05).

Sonuç: Kardiyak arrest sonrası kardiyopulmoner resüsitasyon işlemi ile spontan kan dolaşımı düzelen hastalarda terapötik hipotermi kullanımının yaşam kalitesinin düzelmesi üzerinde önemli ve olumlu etkileri olduğunu düşünüyoruz.

Anahtar sözcükler: Kardiyopulmoner resüsitasyon, normotermi, terapötik hipotermi

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Introduction

Cardiovascular causes are important amidst the causes of death in the world and our country. The fundamental problem is neurological damage after successful cardiopulmonary resuscitation (CPR) in cardiac arrest. Consequently, the prognosis is impaired, which is causing increased mortality and morbidity. The recovery rate of survivors without neurological sequelae is 10-20%.[1] There is a continuous deliberation over therapeutic hypothermia (TH) in the literature, and the datasets suggest that TH alters neurological results positively and increases survival.[2] The prior experiences in the 1950s provide information on spontaneous circulation after cardiac arrest and the methodological progress in providing TH to the patients.[3,4] However, the benefits were not adequately determined, and there was difficulty in implementing TH to provide beneficial outcomes after this procedure.[5] The application of hypothermia and administration of hypothermic irrigation of blood and fluids periodically are practiced not solely after resuscitation, plus during open-heart surgeries, primarily in the cardiopulmonary bypass period using a heart-lung machine.[6] Particularly, patients enduring aortic surgery are systemically cooled.[7]

In this retrospective study, we endeavored to discuss our data in a patient population diagnosed with cardiac arrest. The patients who returned successfully to spontaneous blood circulation after CPR were applied to normothermia or TH. Results were analyzed according to our hospital study protocol. During this treatment methods, we compared several parameters, including demographic data, comorbid diseases, possible cause of cardiac arrest, cardiac arrest rhythm, spontaneous blood circulation return time (ROSC), Glaskow Coma Scale (GCS), deep tendon reflex, brain stem reflex, the duration of intensive care unit (ICU) stay, and complications.

Methods

This study was retrospectively conducted between the period of January 1, 2014 and September 1, 2019. This retrospective clinical interventional study was performed in a single-center. During this period, a total of 69 patients were identified to have ROSC after a CPR procedure in our hospital. Preceding the study, Local Ethical Committee approval was obtained by the rules of the Helsinki Declaration (Local Ethical Committee No: 2019/25). The data were collected from patient records and the hospital automation system. TH was administered in 32 patients (Group 1) and 37 patients were in normothermia and did not receive TH (Group 2). The parameters between the groups were compared. TH was applied by the use of special device for cooling procedure. This device was brought to our hospital in 2017. We analyzed that the data collected using TH with this device during the period of 2017-2019. Before 2017, patients were not administered TH. We included these patients in the 2014-2017 period as the normothermia group.

In the evaluation process of the retrospective data for inclusion into the study protocol, patients who had one of the following criteria were excluded from the study and these are as follows: Patients under the age of 18, cardiac arrest with an unknown duration or start time, neurological dysfunction, intracranial bleeding before cardiac arrest, the recorded body temperature below 30°C, CPR time above 60 min, systolic blood pressure below 80 mmHg despite inotropic therapy, and patients with intra-aortic balloon pump. In addition, patients who have a terminal illness and coagulopathy were excluded from the study. Pregnant women and patients whose data could not be reached were also excluded from the study.

Demographic data of all patients regaining spontaneous blood circulation after CPR or patients that required TH, comorbid diseases, cause of arrest, arrest rhythm, ROSC, GCS, the examination of the deep tendon reflex, and brain stem reflex were recorded. Deep tendon reflex and brain stem reflex evaluations were performed after CPR and ROSC. According to the routine procedure applied to all patients, invasive arterial pressure measurements, heart rate, electrocardiography, pulse oximeter, and peripheral oxygen saturation were monitored in the ICU. Informed consent form was obtained from the relatives of patients during admission to the ICU for treatments and procedures. The central temperature monitoring (esophagus, bladder, and rectal) was performed in all patients. Arterial blood gas and laboratory follow-ups were examined. Acute Physiology and Chronic Health Evaluation Score II (APACHE II) score was clinically provided, and it consisted of three parts: 12 different acute physiological variables, age, and chronic health status. APACHE II scores of all patients were calculated. Complications were recorded in the first 24 h. In our hospital, TH was initiated within the first 2 h in patients after ROSC. In the patients with TH, the time to reach the target temperature, the duration of stay at this temperature, and the time to reach to the normothermia were recorded. Gaymar MediTherm Hyper/Hypothermia System (Stryker, Kalamazoo, MI, USA) cooling wraps were used to provide hypothermia. The temperature was targeted as 32-34°C. Midazolam (Sedazolam, Monemfarma Pharmaceutical Industry, Turkey) infusion (2-10 mg/h) or thiopental sodium (Pental Sodyum, Ibrahim Etem Pharmaceutical Industry, Turkey) infusion (0.1-0.2 mg/kg/min) was provided for sedation as well as fentanyl (Talinate, Vem Pharmaceutical Industry, Turkey) infusion (25-100 mcg/h) if required. When the patients had tremors, rocuronium (Myocron, Vem Pharmaceutical Industry, Turkey) was administered intermit-

Table 1. The comparison of the demographic data and co-morbidities

Parameters	Group 1 (n=32)		Group 2 (n=37)		p*
	n	%	n	%	
Age (years) mean±SD	57.46±11.11		61.83±10.59		0.142
Gender					
Woman	9	28.1	12	32.4	0.698
Male	23	71.9	25	67.6	
Weight (kg) mean±SD	80.28±14.88		77.46±13.72		0.416
Height (cm) mean±SD	171.41±5.48		168.68±8.35		0.119
Hypertension	14	43.8	23	62.2	0.126
Diabetes mellitus	7	21.9	11	29.7	0.459
Coronary artery disease	7	21.9	13	35.1	0.226
Cerebrovascular disease	3	9.4	2	5.4	0.526
Aortic stenosis	2	6.2	4	10.8	0.503
Cigarette	18	56.2	19	51.4	0.684
EF (%) mean±SD	45.78±6.10		44.46±7.71		0.438
COPD	2	6.2	4	10.8	0.503
Out-of-hospital cardiac arrest	26	81.2	23	62.2	0.081
In-hospital cardiac arrest	6	18.8	14	37.8	0.081
Cardiac arrest initial rhythm VF	25	78.1	19	51.4	0.021
Cardiac arrest initial rhythm asystole	6	18.8	17	45.9	0.017
Cardiac arrest initial rhythm VT	1	3.1	1	2.7	0.917
The reasons of cardiac arrest					
Myocardial infaction	25	78.1	29	78.4	0.980
Respiratory insufficiency	4	12.5	5	13.5	0.901
Pulmonary emboli	3	9.4	3	8.1	0.853
ROSC (minute) (mean±SD)	31±14.54		26.27±20.03		0.272
Brain stem reflex	5	15.6	10	27.0	0.252
Deep tendon reflex	3	9.4	10	27.0	0.061
GCS (Hospitalization) mean±SD	3.28±0.68		3.81±1.82		0.126

*p<0.05 significant; SD: Standard deviation; EF: Ejection fraction; COPD: Chronic obstructive pulmonary disease; VF: Ventricular fibrillation; VT: Ventricular tachycardia; ROSC: Time to return of spontaneous circulation; GCS: Glasgow coma scale.

tently at a bolus dose of 0.6 mg/kg intravenously as a neuromuscular blocker. The sedation protocol was also applied with the same agents in the normothermia group. Neuromuscular agent was not used in the normothermia group.

Following the end of TH, the hourly warming rate of the device used for restoring the patient's heat to normothermia was at a level of 0.25°C. The same device that is used for patient cooling was used for rewarming. The duration of ICU stay and mechanical ventilation time was recorded. The development of severe complications or mortal status and transfer to inpatient clinic was recorded.

Statistical Analysis

We performed our statistical analysis using SPSS 21.0 (Statistic Inc. Version Chicago, IL, USA) software. Statistical analyses were carried out using the Statistical Package SPSS version 21.0. We presented our data after having an analysis for normal distribution. As our data were normally distributed, we presented our data in the way of mean with standard deviation. Therefore, we analyzed continuous variables using two-tailed t-tests. Nominal variables were provided in the form of number of patients and percentages related to the group they belong. We analyzed categorical variables using Chi-square or Fisher's exact test. We considered statistically significant when $p<0.05$ at a confidence interval of 95%.

Results

The study was conducted on a total of 69 patients, including 21 women and 48 men. There was no statistically significant difference between age, gender, comorbid diseases, reasons of cardiac arrest, and ROSC in both groups ($p>0.05$) (Table 1).

In the group with TH (Group 1), the starting time of TH was recorded as 23.8±3.45 h, and the target temperature

Table 2. The comparison of the intensive care unit findings and complications

Parameters	Group 1 (n=32)		Group 2 (n=37)		p*
	n	%	n	%	
Extubation time (days) mean±SD	4.74±2.80		9.55±10.16		0.035*
ICU duration (days) mean±SD	7.96±5.1		13.4±11.4		0.026*
Inotropic infusion therapy	26	81.2	31	83.8	0.782
Glasgow coma scale (at discharge) mean±SD	12.90±3.64		10.82±4.98		0.133
APACHE 2 Score mean±SD	26.3±6.4		26.30±6.7		0.976
SOFA Score mean±SD	9.34±2.6		9.54±2.3		0.735
Epileptic seizure activity	6	16.2	15	46.9	0.006*
Arrhythmia	5	15.6	7	18.9	0.719
Bleeding	8	25.0	3	8.1	0.056
Hyperglycemia	5	15.6	12	32.4	0.106
Pneumonia	11	34.4	14	37.8	0.765
Sepsis	4	12.5	5	13.5	0.901
Bradycardia	8	25.0	8	21.6	0.740
Renal Insufficiency	4	12.5	9	24.3	0.210
Hyperthermia	7	21.9	9	24.3	0.810
Mortality	14	43.8	23	62.2	0.126

*p<0.05 significant; SD: Stardard deviation; ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment.

achievement time was 5.7±1.7 h. The stay at the target temperature was 23.81±3.45 h, and the time to reach the level of normothermia which is 36.5°C was within 14.84±1.60 h. The recorded highest temperature was in our normothermia group and this was observed in a male patient at age of 65 years old with a value recorded as 39.8°C.

The agents used when sedation was required in Group 1 were as follows: Intravenous midazolam infusion was used in 8 patients (25%), intravenous midazolam and fentanyl infusions were used in 18 patients (56.25%), and intravenous thiopental sodium infusion was used in 5 patients (15.62%). Sedation was not required in 1 patient (3.13%). The use of sedative agents in the normothermia group (Group 2) was as follows: Intravenous midazolam infusion was used in 9 patients (24.32%), intravenous midazolam and fentanyl infusions were used in 20 patients (54.05%), and intravenous thiopental sodium infusion was used in 6 patients (16.22%). Sedation was not required in two patients (5.41%). When the sedative agents used between the two groups were compared, no statistical difference was found (p>0.05). In addition, rocuronium was used as a neuromuscular agent to prevent tremor in 87.5% of the patients in the hypothermia group.

The recorded data in ICU, follow-up parameters, inotropic infusion therapy, GCS (at discharge), and complications of the two groups are summarized and compared in Table 2. As a result of the analysis, it was discovered that the extubation time of the patients who underwent TH (Group 1) (4.74±2.80 days) was statistically significantly lower than the extubation time of the patients with normothermia (Group 2) (9.55±10.16 days), (p<0.05). In addition, the length of stay in the ICU (7.96±5.10 days) of the patients who underwent TH (Group 1) was statistically significantly lower than the length of stay in the ICU of patients with normothermia (13.40±11.40 days) (Group 2) (p<0.05). Finally, the number of patients with epileptic seizure activity in Group 1 was n=6 (16.2%) whereas, it was n=15 (46.9%) in Group 2, and this difference was statistically significant (p<0.05). The Glasgow coma scale evaluated at discharge was higher in the TH group of patients but statistically significant difference was not observed between the two groups (12.90±3.64, 10.82±4.98, respectively, p>0.05). Bleeding was also higher in the TH group (Table 2). In contrast, no notable differences were observed between the two groups regarding ICU follow-up parameters and complications other than those mentioned (p>0.05) (Table 2).

Discussion

The purpose of successful CPR after cardiac arrest is to continuously provide comprehensive support to improve vital organ perfusion and cardiopulmonary functions. For this purpose, it should be with professional multidisciplinary cooperation.[8] TH is a valuable treatment approach for protecting the brain and other organs. That technique improves life expectancy and quality in these patients. It is an effective treatment method for preventing chemical reactions with reperfusion damage after arrest and suppressing cerebral metabolic activity.[2] The body's central temperature below 35°C is defined as hypothermia. TH is broadly practiced between 32 and 34°C.

It is critical that cardiac arrest cases are witnessed inside or outside the hospital.[9] This allows us to obtain more accurate data about the time of arrest and the time of spontaneous circulation returns. This also helps to predict our expectations of the patient after the treatment. Our results from this retrospective clinical study revealed that; the number of patients who developed cardiac arrest outside the hospital was higher in the TH group (Table 1).

Ventricular fibrillation (VF) is the rhythm pattern detected widely in all cardiac arrest cases.[10] There are studies on TH according to the initial rhythm of cardiac arrest in the literature.[2,11,12] In some of these studies, the initial cardiac arrest rhythm was included only as VF, while all rhythms were included in others. In our study, patients with every rhythm were included; the most common rhythm in both groups was VF (Table 1). There was also no statistically meaningful difference between the groups according to the initial rhythm of cardiac arrest.

The starting TH as soon as possible after the spontaneous blood circulation returns is necessary to provide maximum benefit. In their study, M Michael R.M and his colleagues reported to a significant conclusion that when the TH starts 1 h later, it has increased the risk of mortality by 20%.[13] In our study, TH was started within the first 2 h after ROSC, TH was applied to patients for a duration of around 24 h (23.8±3.45 h) and the time to reach normothermia was 14.84±1.60 h.

For TH, some methods can be used to achieve the targeted temperature. It is one of the methods to increase heat loss with peripheral vasodilation and to reduce heat production by preventing tremors. The prevention of tremors can be realized by neuromuscular blocking. The depression of the heat regulatory center in the hypothalamus can also be arranged with anesthetic agents.[14] In a systematic review of 44 studies examining sedation protocols in patients with spontaneous circulation after cardiac arrest, it was reported that midazolam and fentanyl were the most common usage.[15] In our study, midazolam and fentanyl combination was the most preferred combination. Rocuronium is also used as a neuromuscular blockage agent. In TH, superficial cooling, cold liquids, and intravenous cooling are used as methods. A literature study in the early 2000s stated that some of the ICUs that did not apply hypothermia in Germany had a cooling technique and needed specific devices. It is reported that the most of the ICUs performing low-cost methods such as superficial cooling and cold liquid infusion.[16] The superficial cooling methods with specific devices were used to reduce the body temperature in practice in our clinic. The targeted central temperature was between 32 and 34°C. The time to reach the target temperature has been a vital factor investigated in the studies. In addition, the duration of the application for hypothermia treatment has been reported. In a nine-center prospective study in which hypothermia was applied with a cold air pumping device to 32-34°C, the target temperature was reached in 4 h and applied for 24 h.[2] In a four-center study, hypothermia was achieved with ice packs placed on the head and trunk. The target temperature was reached in 2 h and the patients were left in hypothermia for 12 h.[11] In a study conducted in 19 centers under the supervision of the European Resuscitation Council, it was published that the target temperature was reached in 150 min with intravascular cooling, 75 min with superficial cooling, and it was applied for 24 h.[12] In our study, the target hypothermia temperature was reached in 5.7±1.7 h, and TH was applied 23.81±3.45 h in patients who underwent TH. These results can be compared with the previous clinical studies.

In the previous studies, it has been reported that several different factors affect the method of TH. These include: (1) The start time of TH is important. It is assumed that the TH application generally starts for most of the patients in 4 h, (2) the use of the additional cooling devices and the use of the cold intravenous fluids may differ between hospitals, (3) the use of different heat targets and starting points has been reported previously, and (4) the hospital admission policies vary between the hospitals. Therefore, it is not easy to compare the start time of TH, and because of the additional cooling devices, the target temperature reaching time during TH varies between a median duration of 2.5 h up to 6 h. The different hospital protocol for hospital admission also affects the starting time of ROSC.[17] In patients with hypothermia, at the end of staying at the target temperature, the patient should be warmed up. Uncontrolled and rapid warming is associated with worse neurological outcomes and increased mortality. Therefore, heating should be achieved slowly and in a controlled manner.[18] The literature states that a warming velocity about 0.25-0.50°C/h is ideal, and the target body temperature value should be 37°C.[19,20] In our patients, the hourly warming velocity was identified as 0.25°C/h. This result is consistent with the values of the previous clinical studies.

TH may have adverse effects on organ systems. According to the results of M. Holzer et al.'s[2] study, pneumonia (37%), arrhythmia (36%), sepsis (13%), kidney failure (10%), pulmonary edema (7%), convulsion (7%), and pancreatitis (1%) in the hypothermia group have been reported.[2] The overall complication rates were 73% in the hypothermia group, 70% in the normothermia group, and there was no statistical difference between the two groups.[2] In addition, the cardiovascular system may be affected. Arrhythmia, bradycardia, and increased systemic vascular resistance may be encountered.[11] Hypothermia may affect the coagulation cascade and cause bleeding.[21] In the study conducted by Arrich et al.[12] the patients who underwent moderate hypothermia after CPR, it was announced that 3% of the patients had bleeding and 6% had arrhythmia as a complication in the first 7 days. In our study, bleeding noticed in patients in the TH group was in 8 patients (25.0%), and arrhythmia was in 5 patients (15.6%) (Table 2). In addition, the rate of hyperglycemia was 15.6%. While epileptic seizure activity was found to be higher in the normothermia group, bleeding was higher in the TH group (Table 2). There was no difference between TH and normothermia groups in terms of other complications (Table 2).

In a prospective observational study on TH, high blood glucose levels and increased insulin requirements were observed in patients during cooling and warming periods. It has also been determined that excessive vacillation in blood glucose levels indicates increased mortality.[22] Furthermore, various studies have shown that high blood glucose levels during TH are associated with poor neurological outcomes and increased mortality.[23,24] Besides, in the application of TH, rapid reaching target values in blood glucose level is associated with better neurological outcomes.[25]

In a randomized clinical study, 136 patients were treated with TH and 137 patients with normothermia, and the results were compared. It was reported that patients who underwent TH have an improvement in neurological functions and decreased mortality. However, there was no difference in the data of 7-day complication rates.[2] In a different randomized study, TH was applied to 43 patients, and normothermia was applied to 34 patients after cardiac arrest. Again, better neurological function and lower mortality rates were observed in those who underwent TH. Besides, no statistically significant difference was detected between them in terms of neurological side effects.[11] In a meta-analysis evaluating 12 non-randomized and two randomized studies, TH was associated with reduced in-hospital mortality.[26] Soleimanpour et al.[27] and Ahn et al.[28] also reported that TH is an effective strategy to improve neurological outcomes after cardiac arrest and CPR.

In our study, GCS evaluated at discharge was higher in the TH patient group and there was no statistically significant difference between groups (Table 2). Epileptic seizure activity was also found less in the hypothermia group. In our study, mortality rates between groups were compared, and no significant difference was found between the two groups (Table 2).

The limitation of our study is the lack of a prospective and randomized study, the small number of patients, and difference in the distribution of the number of in-hospital and out-of-hospital cardiac arrest patients in the groups.

Conclusion

The use of TH in patients provided significant results like shorter extubation time and ICU stay and fewer complications. Neurological evaluation of patients who faced cardiac arrest and applied TH is better than normothermic patients. However, the study needs to be performed on a larger group of patients to provide satisfactory data on cardiac arrest-related patients and an improvement in the rate of complications observed after cardiac arrest and CPR.

Disclosures

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