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Therapeutic Hypothermia for Hypoxic-Ischemic Encephalopathy: Current Experience of a Turkish Tertiary Center

Yenidoğanda Hipoksik İskemik Ensefalopati Tedavisinde Hipotermi Uygulaması: Tek Merkez Deneyimi

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ABSTRACT

Aim: We conducted a study to demonstrate the effect of early initiation of cooling in newborns with Hypoxic-ischemic encephalopathy (HIE), before and during their transport to a cooling center.

Material-Method: A total of 32 outpatient neonates were enrolled in the study. Because of the implementation of a new local guideline concerning the preparation and transport of neonates who are therapeutic hypothermia (TH) candidates, the data gathered belonged to two distinct patient groups; Group I (before guideline, n=18) and Group II (after guideline , n=14).

Results: With respect to clinical characteristics, application of TH and conservative therapies both groups were similar. The frequency of observed clinical seizures, the occurrence of an abnormal electroencephalography (aEEG) and the mean body temperature of the outborn infants at their admission were all lower in Group II. With respect to mortality, the mortalities of Group I and Group II were 44.4% and 21.4% respectively and except hypotension, all complications were less frequent in Group II. An organized team approach with early cooling is important for the success of TH.

Conclusion: We found that with education, our referring and transport physicians can initiate and maintain TH for neonates before and during their transport.

Keywords: Hypothermia; hypoxia-ischemia; brain / therapy; newborn; patient transport

ÖZET

Amaç: Çalışmanın amacı hipotermi uygulama merkezine transport edilmeden önce ve transport sırasında erken soğutma başlanmasının etkilerini araştırmaktır**.**

Gereç ve Yöntem: Değerlendirmeye 32 yenidoğan bebek alındı. Tedavi amaçlı hipotermi uygulamasına aday yenidoğan bebeklerin transport ve hazırlanmasında yeni bölgesel rehberin etkilerini araştırmak için bu rehberin kullanılmasından önce (n=18) ve sonra (n=14) kabul edilen yenidoğan bebekler çalışmaya dahil edildi.

Bulgular: Her iki grupta da sırasıyla klinik özellikler hipotermi uygulaması ve diğer tedaviler benzerdi. Lokal rehberin kullanıma girmesinden sonra hastanemize dış merkezlerden kabul edilen bebeklerde (grup II) klinik nöbet, anormal electroensefalografi (aEEG) bulgusu ve geliş ortalama vücut sıcaklığında artış saptandı. Mortalite oranları GrupI'de %44.4 ve Grup II'de %21.4 olarak hesaplandı. Hipotansiyon dışında tüm komplikasyonların sıklığı GrupII'de daha az bulundu. Başarılı tedavi amaçlı hipotermi için organize ekip yaklaşımı önemlidir.

Sonuç: Sevk eden ve transfer eden ekiplerin eğitimi ile yenidoğanların transport öncesi ve sırasında hipotermi başlanabilir ve sürdürülebilir.

Anahtar kelimeler: Hipotermi, hipoksi-iskemi beyin / tedavi, yenidoğan, hasta nakli

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Introduction

World Health Statistics 2011 presents that the percentage of birth asphyxia as a cause of death among children may reach as high as 29% (1). According to another report, one quarter of the neonatal deaths annually are caused by perinatal asphyxia (2). Perinatal hypoxic–ischemic encephalopathy (PHIE) is defined as brain injury occurring as a result of the combination of inadequate blood flow and oxygen delivery to the newborn's brain. PHIE is associated with both short- and long-term adverse effects on mortality and neurodevelopmental outcome of the neonate. Outcome statistics for PHIE state that approximately 15% of these cases will die in the neonatal unit, 10–15% will suffer from cerebral palsy, and up to 40% will develop other neurological disabilities and behavioral problems (3, 4).

The reported incidences of PHIE from different centers in Turkey are between 2.6–10.0 per 1000 term infants (5-7). During the year 2009, neonatal mortality rate was 10 per 1000 live births in Turkey and perinatal asphyxia was the 3rd leading cause of mortality (6.1%) in the early neonatal period (8).

The results of several randomized controlled trials (RCT) support the safety and efficacy of "therapeutic hypothermia" (TH) in decreasing mortality and disability rates in infants with PHIE (9-13). Although TH is now an evidence-based therapy it must be borne in mind that despite the use of TH, more than 40% of the treated infants died or survived with disabilities in these trials. The efficacy of TH seems to be closely related to the starting time of cooling, the absence of fluctuations in the target temperature during the intervention period and the execution of the rewarming process in the correct time. Therefore, for the safe and effective implementation of TH guidelines are needed.

In this report, we summarized our results and experiences concerning the use of TH for the treatment of PHIE.

Material Method

The infants who received Whole Body Therapeutic Hypothermia (WBTH) for PHIE in our neonatal intensive care unit (NICU) between June 2008 and January 2012 were recruited. Based on the results of the three large RCTs, local ethics committee approval was received for the implementation of WBTH to neonates with PHIE.

A new local guideline concerning the preparation and transfer of neonates who are TH candidates was put into use in January 2011. Consequently, a local information and training meeting was held in March 2011. The aims of the meeting were to optimize and standardize the medical care of the infants with PHIE who are potential candidates for WBTH during their initial care and transfer. A total of 49 healthcare professionals from Ankara and neighboring provinces attended this meeting. As our ambulances do not possess the technologies required for active cooling and rectal temperature monitoring, the passive cooling protocol described by Giles S Kendall and colleagues were implemented to be used before and during the transfer of the infants (14). Therefore, the data gathered belonged to two distinct time periods; the first one being June 2008 and January 2011 period ("Group I, before guideline") and the second one being March 2011 and January 2012 period ("Group II, after guideline").

In our NICU, the TOBY Study sequential inclusion criteria is used for making a decision of treatment with WBTH (12) whereas the severity of PHIE is assessed according to the Sarnat and Sarnat's Staging System (15).

The amplitude-integrated electroencephalography (aEEG) of the infants were performed using the cerebral function monitor "OLYMPIC CFM 6000å" (Olympic Medical, Seattle, Washington, USA). For the interpretation of the aEEG recording, the normal recording was accepted as a dense band of aEEG activity with an upper margin of >10 µV and a lower margin of >5 µV (165). The aEEG tracing was classified as abnormal if the upper and/or lower margins of the dense band of aEEG activity were outside the depicted normal values or if a seizural activity was identified. The aEEG of every infant was continuously recorded for the first seventy two hours of their lives.

WBTH with Tecotherm^{å} (Inspiration, Leicester, UK) was implemented on the occasion of an abnormal aEEG tracing and/or a witnessed clinical seizure within the first six hours of the infants lives. By manually adjusting the perfusion temperature, active cooling was achieved which allowed the rectal temperature of the infants to decrease to 33-34 °C within 60 minutes. The duration of hypothermia was constant at 72 hours and at the end of this period, the temperature was manually increased by increments of 0.5 °C per hour. The goal temperature at the end of the rewarming period was 36.5 °C. The infants' body temperatures were both monitored and recorded simultaneously with rectal and skin probes.

Conservative management of the infants with PHIE were according to our NICU's usual practices. Clinical and electrographic seizures were taken under control by phenobarbital and phenytoin as first- and second-line treatments, respectively. The first cranial ultrasonography was performed during the first seventy two hours and repeated as indicated thereafter. Following discharge, the infants were followed at our neonatal neurology and developmental pediatrics clinics. The neurodevelopmental status of the infants was evaluated at 18 months of age using the Bayley Scales of Infant Development II (BSID-II).

Statistical analyses were performed using the software SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The results are presented as numbers (n), frequencies (%), means with respective standard deviations (SD) and medians. Continuous variables were compared with t-test or Mann-Whitney U test between independent groups and with Wilcoxon test between two dependent groups. The statistical significance level was set at 5% ($p<0.05$).

Results

During the time between June 2008 and January 2012, 75 newborns were hospitalized with a diagnosis of PHIE. Thirty two of these neonates who transferred our hospital for and received WBTH were divided into two groups (Group I n=18, Group II n=14) as previously described. The neonatal demographic, clinical, and laboratory characteristics of the infants in Group I and Group II are summarized in Table 1 whereas the important characteristics of the WBTH period are given in Table 2. The major complications and the mortality observed in both groups are depicted in Table 3.Although both groups were similar with respect to the frequencies of severe PHIE (Group I 66.6%, Group II 64.2%, $p>0.05$), the frequency of observed clinical seizures was significantly lower in Group II (Group I 100.0%, Group II 50.0%, $p<0.001$). To note, despite not reaching statistical significance, the occurrence of an abnormal aEEG was again lower in Group II (Group I 77.0%, Group II 50.0%, $p=0.72$). Also the mean body temperature of the outborn infants at their admission was significantly lower in Group II (Group I 36.7±0.5°C, Group II 34.6±0.5°C, $p=0.02$).Except hypotension, all complications were less frequent in Group II (Tables 2).With respect to mortality, the overall mortalities of Group I and Group II were 44.4% and 21.4% respectively ($p=0.18$). In Group I, mortality among the inborn infants was 35.7% while the outborn infant mortality was 75.0% ($p=0.27$). In Group II, the inborn and the outborn infant mortalities were found to be 33.3% and 0.0% respectively ($p=0.25$). When the inborn infant mortality values of Group I and Group II were compared, statistically similar results were obtained (Group I 35.7%, Group II 33.3%, $p=1.0$). On the contrary, the outborn infant mortality was significantly lower in Group II than in Group I (Group II 0.0%, Group I 75.0%, $p=0.048$). The most common cause of death was multiorgan failure. The neurodevelopmental outcome in surviving infants of Group I were evaluated only. The median scores for Mental Developmental Index and Psychomotor Development Index were found to be 100 and 97 respectively.

Table 1: Neonatal demographic, clinical, and laboratory characteristics

Characteristics		Group I (n:18)	Group II (n: 14)	*p*
Gestational age, wk*		39.5 ± 1.4	39.1 ± 1.2	NS
Birth weight, g		3348 ± 341	3115 ± 360	NS
Male, n(%)		9 (50)	10 (71.4)	NS
Outborn, n(%)		4 (22.2)	5 (35.7)	NS
Apgar score at 5 min,		1.5 ± 1.1	1.5 ± 0.8	NS
Apgar score at 10 min,		3.1 ± 1.0	3.0 ± 1.6	NS
Cesarean section, n(%)		13 (72.2%)	10 (71.4%)	NS
Umblical pH*		6.9 ± 0.4	6.9 ± 0.1	NS
Umblical base defisit*		13.5 ± 6.1	20.3 ± 4.8	NS
Severe HIE, n(%)		12 (66.6%)	9 (64.2%)	NS (p=1.0)
Clinical seizure, n(%)		18 (100%)	7 (50%)	<0. 001
Abnormal aEEG, n(%)		10 (77%)	7 (42.8%)	NS (p=0.72)
Temperature at admission	outborn	36.7.0± 0.5	34.6 ± 0.5	0.02
	Inborn	34.2 ± 1.3	35 ± 0.7	0.09

Table 2: Details of intervention period

Details		Group I (18)	Group II (14)
Age at start cooling, minutes	Outborn	255 (240-300)	180 (60-240)
	Inborn	120 (50-360)	60 (30-240)
Abnormal Cranial Ultrasonography, n(%) • Grade II hemorrhage • Grade III hemorrhage • Ischemic findings		 4 (22.2) 0 2(11.1)	 2(11.8) 0 1 (5.9)
Anticonvulsantherapy,n(%) • Single drug • ≥1 drugs Adverse effects		 10 (55.5) 5 (27.7)	 4 (28.5) 4 (28.5)
• Systemic hypotension*		5 (27.8)	7 (50)
• Bradycardia, n(%)		8 (44.4)	2 (14.2)
• Need for nitric oxide		3 (16.6)	2 (14.2)
• Thrombocytopenia, n(%)**		5 (27.8)	1 (7.1)
• Hypoglycemia, n(%)		5 (27.8)	2 (14.2)
• Subcutan fat necrosis		1 (11.1)	0
• Renal failure, n(%)π		4 (22.2)	1(7.1)
• Abnormal liver function		15 (83.3)	11(78.5)

* mean blood pressure<40 mmHg

**platelet count < 100.000 cells per µl

π required peritoneal dialysis

Table 3. The major complications and the mortality rate in both groups.

	Group I		Group II		*p value*
	Death	Survivor	Death	Survior	
Mortality					
Inborn	5*	9	3*	6	0.9*
Outborn	3*	1	0*	5	0.048*
Other complications					
Stage III encephalopathy	6*	6	1*	8	0.49
Renal failure, dialysis	2*	2	1*	0	1.0
Clinical seziure	8	10	3	4	0.04

Discussion

According to the report of the Turkish Neonatal Society Hypoxic Ischemic Encephalopathy Study Group, the incidence of PHIE is 2.6 per 1000 live births and the mortality is 22.6% (6). In an another study from Turkey, PHIE incidence is reported to be 10.0 per 1000 live births and the mortality rate is 38.0% (5). Physicians caring for infants with PHIE usually report the clinical findings of these infants as modified Sarnat scores. Neonates with lasting Sarnat Stage III (severe) encephalopathy carry an important risk of death and a highly increased risk of severe disability approaching 100% among the survivors. Sarnat Stage II (moderately severe) patients are less likely to suffer from severe impairment but will have more deficit than both mild encephalopathy patients (Sarnat Stage I) and normal infants (Sarnat Stage 0). According to the results of large case series from Turkey, the frequencies of the neonates with PHIE according to their Sarnat Stages are as follows: Sarnat Stage I 7-43%, Sarnat Stage II 25-45%, and Sarnat Stage III 21-34% (11-13). In none of these studies TH was implemented and the mortality rate for Sarnat Stage III patients was reported to be between 51.7% and 83.0% (11-13). Our series relatively higher Sarnat Stage III frequency of 65% is possibly related to both Perinatology center and tertiary NICU center properties of our hospital. If both of our groups (Group I and Group II) are taken into account, the mortality rate for Sarnat Stage III patients treated with WBTH is 33.0%. This significantly lower mortality rate supports the view that WBTH is an effective treatment for PHIE.

A number of experimental studies and clinical RCTs about PHIE documented a substantial beneficial effect with induction of TH of only a few degrees (i.e., "mild" hypothermia) (9-13). Even so, the American Academy of Pediatrics Committee on the Fetus and Newborn commented that, "TH should be considered investigational until the short-term safety and efficacy have been confirmed in the additional human trials underway" (17). More recent meta-analyses showed that TH is remarkably safe and significantly improves the prognosis for infants with PHIE (18,19). The mechanisms underlying these beneficial results may include reduced neuronal metabolic demand, reduced cytotoxin accumulation and prevention of apoptosis during secondary energy failure (9,10).It is of great importance that TH should be started before the onset of secondary energy failure and the excitatory features, especially the seizures. This therapeutic window lasts for approximately 6 hours and the duration of this latent phase between primary and secondary energy failure is inversely proportional to the gravity of the hypoxic-ischemic insult. So, timing of induction of TH after PHIE is critical. Another important issue with TH seems to be the cooling system. Ideally, it should induce rapid cooling to the target temperature both without overcooling and without temperature fluctuations (13,14). Similarly, rewarming should be achieved without fluctuations and overheating. Nevertheless, overcooling and overheating are frequently encountered problems. The median time for the arrival of the transferred patients in our study was 4.3 hours and their mean body temperature was 36.1 °C. On reaching the target temperature with active cooling in an hour, the initiation time of TH has reached 5.3-6.0 hours. Regrettably, studies have documented that TH started after a seizure or later than 5.5 hours showed decreased efficacy (20). The TOBY study also showed that infants treated within 4 hours of delivery benefit the most from TH (12). As expected, our mortality rate for the outborn neonates in Group I was higher.

If the process of cooling is deferred until the arrival of the infant at a cooling center, this likely reduces efficacy. So the management of the transfer is of grave importance. Kendall stated that "Passive cooling with appropriate monitoring is a simple and effective technique to initiate therapeutic hypothermia outside a cooling centre" (14). Some recently completed clinical RCTs in which babies were cooled during transport will provide valuable information about this practice (14). We also saw that with education and practice, our referring and transport physicians can initiate and maintain TH for neonates before and during their transport. Lower body temperatures which may offer a neuroprotective effect can be achieved several hours sooner with this approach.

The practice of TH should be further evaluated, as should be the management of the transfer of the neonates who are candidates for TH.

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