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Passive Therapeutic Hypothermia during Transfer of Hypoxic-ischemic Newborn: Evidences and feasibility from a Neonatal Emergency Transport Service.

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ABSTRACT

Perinatal hypoxic-ischemic events are important cause of mortality and morbidity worldwide. Recently, the use of mild-moderate hypothermia in such newborn showed improvement in both survival and neurological outcomes. Not all birth centers are equipped for hypothermic treatment and the neonate needs to be transferred to a referral center to receive the treatment.
Aim of our study is to evaluate feasibility of a Neonatal Transport Emergency Service to safely transfer newborns with hypoxic-ischemic encephalopathy in passive cooling to the referral center.
Methods: data of transport for perinatal asphyxia have been extracted from transport database of Federico II University Hospital. We analyzed safety and efficacy of neonatal transport with passive cooling by means of activation time, transportation time, capability to transfer the neonate within six hours of life and reaching and keeping a body temperature of 33-35° C .
Results: activation time was shorter than 30 minutes in 93.3% cases. Transportation time was shorter than 120 minutes in 45.3% of cases. Any case of overcooling or adverse events related to passive cooling were not detected. Neonates arrived in referral NICU within 6 hours in 65/67 cases. At the receiving center, 70% of neonates had temperature between 33 -35°C.
Conclusion: passive cooling during neonatal transport is feasible with no adverse events. These results may rise the question if the use of specific mattress for neonatal therapeutic active hypothermia may improve the rate of neonates transferred with body temperature between 33 – 35°C; we believe that this could be a crucial point considering the beneficial role of therapeutic hypothermia started within 6 hours from birth of a neonate with hypoxic-ischemic encephalopathy.

Keywords: hypoxic-ischemic encephalopathy, neonate, hypothermia, neonatal transport

SOMMARIO

L'encefalopatia ipossica ischemica da asfissia alla nascita è tra le principali cause di mortalità e morbilità con esiti permanenti. Recentemente, il trattamento ipotermico del neonato asfittico ha dimostrato di migliorare sopravvivenza ed outcome neurologico a distanza. Sfortunatamente, non tutti i centri sono attrezzati per fornire tale trattamento per cui centrale è il ruolo del servizio di trasporto neonatale che ha il compito di trasferire i neonati necessitanti trattamento ipotermico verso la TIN di riferimento.
Lo scopo dello studio è stato quello di valutare la fattibilità di trasferire in ipotermia passiva i neonati con encefalopatia ipossico-ischemica verso la TIN di riferimento.
Metodi: i dati sono stati ricavati dal database del Servizio di Trasporto Neonatale dell'Università Federico II di Napoli. Abbiamo rilevato la sicurezza e l'efficacia riguardo il trasporto di neonati in ipotermia passiva attraverso il calcolo del tempo di attivazione, di trasporto, capacità di trasferire il neonato entro le 6 ore di vita e raggiungere e mantenere durante il trasporto una temperatura corporea tra 33-35° C .
Risultati: il tempo di attivazione è stato < 30 minutes nel 93.3% dei casi. Il tempo di trasporto è stato < 120 minuti nel 45.3% dei casi. Nessun caso di overcooling o di evento avverso è stato associato al trasporto in ipotermia passiva. I neonati sono arrivati in TIN entro 6 ore dalla nascita in 65/67 casi ed il 70% di essi all'arrivo in TIN aveva una temperatura corporea tra 33 -35°C.
Conclusione: l'ipotermia passive durante il trasporto del neonate con encefalopatia ipossico-ischemica è fattibile senza importanti eventi avversi. Piuttosto questo studio deve far ragionare se l'utilizzo di specifici materassini per indurre una ipotermia attiva controllata durante il trasporto possano migliorare il tasso di neonati che giungono nella TIN referente con temperatura tra 33 – 35°C. Riteniamo che questo possa essere un punto cruciale considerando l'effetto benefico dell'iniziare un adeguato trattamento ipotermico entro 6 ore dalla nascita nel neonato con encefalopatia ipossico-ischemica.

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INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is an important cause of mortality and morbidity worldwide, involved in cerebral palsy of infancy and disabilities. Moderate- severe HIE leads to a mortality in 10-60% of patients and neurological impairment in 25% of survivors[1]. Incidence of HIE is 1-2 on 1000 alive newborn and higher in developing countries, except for pre-conception abnormalities and/or ante-partum factors[2,3].

Just a few years ago, newborn with HIE accessed only to palliative-supportive care in NICU, without a specific neuroprotective treatment. Recently, scenario changed radically, thanks to the use of mild-moderate hypothermia in asphyxia, improving both survival and neurological outcome at 18 months of life[4,5]. Therapeutic hypothermia acts through different patterns, including reduction of brain metabolism and vasogenic edema, release of excitatory neurotransmitters and oxygen free-radicals, cytokine activation pathways[2].

The above-mentioned treatment presents strict chronological limitations to be useful, the so-called "therapeutic window", which lasts six hours until the asphyxia insult[6] that is why experts' agreement suggest beginning the treatment as soon as possible[7]. Recommendations for the management of newborns eligible for therapeutic hypothermia, drafted by Italian Society of Neonatology (SIN)[8,9], second edition, state that treatment has to be performed only in NICU, where highly specialized nurses and expert neonatologists are available[8,9]. However, hypoxic event is often unpredictable, not related to specific risk factors, mandatory for a recommended delivery in Level III hospital with NICU. Neonatal Transport Emergency Service (NETS) is an essential tool to ensure hypothermic treatment to every newborn eligible, wherever they are. Some NETS ambulances are NICU on wheels with all the equipment needed for emergency assistance of neonate even ecography[10] and mattress for active hypothermia. Although the greater part of neonatal transfers depends to prematurity, respiratory distress, infectious diseases, feeding intolerance, hyperbilirubinemia[11,12] some of them are driven by an unexpected prenatal hypoxia. On one hand, Level I-II centers must detect as soon as possible newborn with HIE and call NETS, and start the passive cooling. On the other, NETS equip must provide therapeutic hypothermia on-going, targeting a body temperature (BT) on 35°C, to avoid over or undercooling[9].

In our region, Campania, three different transporting services (belonging to University Hospital of Naples "Federico II", Hospital "Santobono" of Naples and Hospital "S. Sebastiano" of Caserta) act simultaneously 24 hours, transporting 1600 neonates per year, serving an area of 13670,95 km2 and a population of about 6 million of inhabitants.

In 2014 neonatal transfer index was about 2.6% in Campania, comparable to past years but over national average of 1.3%. Our NETS Federico II provides half of regional transports (about 800 per year).

OBJECTIVE OF THE STUDY

Aim of our study is to evaluate feasibility of a NETS service to safely transfer newborns with HIE in passive cooling.

METHODS

We realized a retrospective study, on a population of out-born neonates, transferred between January 2012 and December 2015. Data of transport for perinatal asphyxia have been extracted by NETS database. Criteria for admission to therapeutic hypothermia were established by 2012 Official Recommendation of Italian Society of Neonatology (SIN)[9]. According to such criteria to identify transported neonates candidates to hypothermic treatment, we evaluated blood gas sample in the first-hour of life (either cordonal or neonatal one) and neurological physical examination of newborn, to state presence and severity of HIE. The evaluations were performed by transferring hospital neonatologists or NETS personnel. The neonates eligible to hypothermic treatment underwent passive cooling during transportation in a level III NICU turning-off the incubator and using also synthetic ice sacks or latex gloves fill with cool water if necessary. Axillary temperature was monitored continuously during transportation.

We analyzed safety and efficacy of neonatal transport followed good clinical standard reported in literature. Indeed, transport services are efficacy in case of:

- Activation time (time from request call to team take off) shorter than 30 minutes in 75% of cases.
- Transportation time (time from request call to arrival at destination in NICU) shorter than 120 minutes in 75% of cases[13].

In addition, dwell time in transferring hospital can be used as measure of time needed to stabilize neonates before leaving.

About efficacy of transfer of neonates affected by HIE on passive cooling, we evaluated if NETS service was able to transfer the neonate with HIE within six hours of life and reaching and keeping a body temperature of 33-35° C during transportation till receiving NICU.

We analyzed registered body temperature (BT) of every patient at leaving and at arrival to destination. Values lower than 33° C have been considered overcooling, while values over 35°C have been considered insufficient for passive hypothermia. We searched also adverse events related to passive cooling (skin lesions).

STATISTICAL ANALYSIS

Quantative continuous variables have been expressed as mean and range (minimum and maximum). T- Student test was performed for analysis. A $p< 0.05$ was chosen as statistically significant. Software Statistical Package for Social Sciences (SPPS), version 18,0 (Ibm, Nt) were used.

RESULTS

Demographic features of our population are summarized in **Table 1**. We enrolled 67 neonates transferred on passive cooling eligible to therapeutic hypothermia. According to SIN Recommendations[8], they were over 35-weeks of gestational age, weighting over 1800 grams, except for one of them, 34-weeks of gestation but weighting 1900 grams. There were in Campania region 50 Level I transferring centers (74,6%), 4 level II (6%) and 13 (19,4 %) and 13 level III centers in the study period. (**Figure 1)**

Ambulance travelled an average distance of 36.5 km (range 0.9 – 150 km) to arrive to the receiving centers from the transferring hospital.

Activation time was registered in 60/67 cases with a mean of 15 minutes. It was shorter than 30 minutes in 56/60 registered cases (93.3%).

Transportation time was detectable in 64/67 cases and mean time was of 138 minutes, and it was shorter than 120 minutes in 29/64 cases (45.3%)

Mean dwell time was of 60 minutes (calculated in 64 on 67 cases).

We did not find any case of overcooling (BT < 33°C) or adverse events related to passive cooling (skin lesions, significant bradycardia or hypothension).

We compared only patients with available BT data both on departure and arrival (50 neonates). In the overmentioned group, mean BT at departure was 35.5°C (max 37.1°C), while mean BT at arrival was 34.8°C (max 36.6°C). During transportation, BT decreased of 0.7°C ($p<0.01$). In both groups, the lowest BT was 33°C. (**Figure 2)**. At the transferring

Table 1. *Demographic characteristics of population*

Total Number	67
SEX	
Female	33
Male	34
TWINS	
Single	65
Bigeminy	1
WEEKS OF GESTATION	
Mean	38,4
Maximun	41
Minimum	34
BIRTH WEIGHT (grams)	
Mean	3150
Maximum	5000
Minimum	1900

Figure 1. *Transferring Units divided by level of assistance*

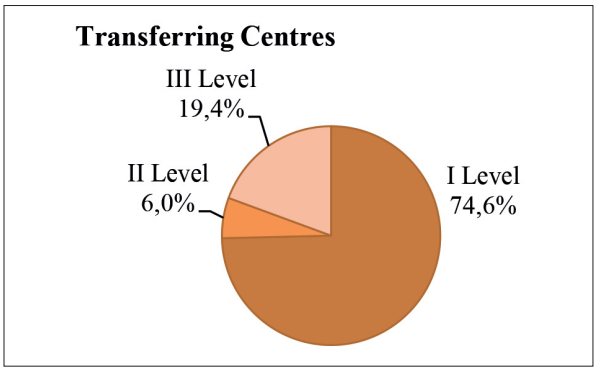
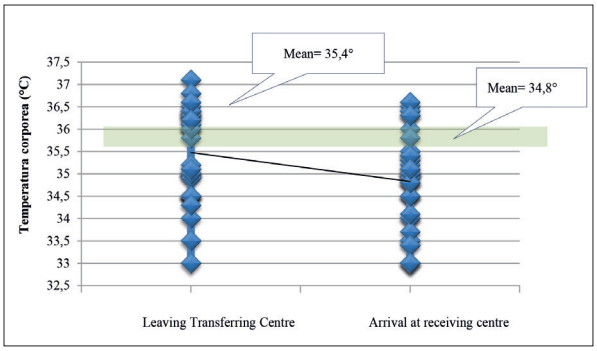


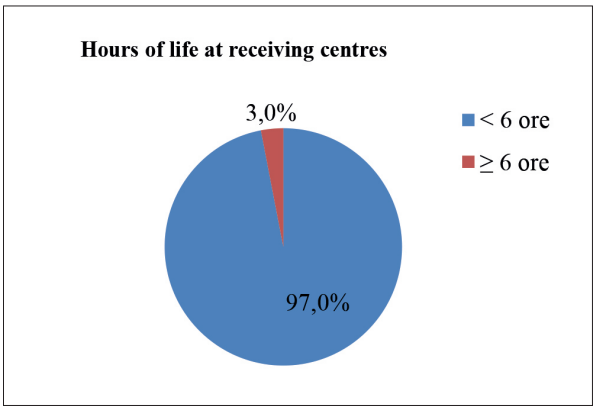
Figure 2. *Body Temperature (BT) (mean and range) at transferring and receiving centres*



center BT was between 33 -35°C for 38,5% of neonates. At the receiving center, 70% of neonates had BT between 33 -35°C.

Mean age of patients at admission in transferring centers was 3 hours (range 55 minutes – 10 h 55 min). Neonates arrived in referral NICU under 6 hours in 65/67 cases (97%) and over 6 hours in 2/67 (3%). The only two patients older than 6 hours, still maintained an ideal BT for passive hypothermia. (**Figure 3)**

***Figure 3**. Neonates hours of life at arrival*



DISCUSSION

HIE is an important cause of mortality and morbidity worldwide. The only neuroprotective treatment now available is cooling affected neonates. It is mandatory to provide this intervention in a specific time-window (until sixth hour of life) and only in NICUs ready for this procedure. When asphyxiated neonates is born in a level I or II hospital, NETS acts a fundamental role in Campania, where there are lots of Level I centers (56 in 2016) and one of the highest birth rate of Italy and, at the same time, highest percentage of neonatal transfer (about 2.6%).

Federico II NETS service is one of three regional neonatal transport service, working 24 hours a day, which manage more than half of total annual transport (about 800 transfer/year).

The aim of this study is to evaluate proficiency of our NETS in safe and effective transferring of neonates with HIE on passive cooling between January 2012 and December 2015.

Our data showed that all of 67 neonates transferred matched inclusion criteria for hypothermic treatment of HIE, except for one patient who was born at 34 weeks of gestation but weighted 1900 grams.

Although nowadays there aren't enough data on safety and benefit of hypothermia in preterms, in literature there are some cases reporting late preterms who underwent hypothermia[14,15], and had an 18-month follow up, showing a normal neurological development[16, 17].

Transferring centers were usually a level I hospitals (74,6%). It means that often in our sample intrapartum asphyxia was unpredictable, in pregnancies without significant risk factors which would have transferred women to a level III hospital with NICU.

In 19.4% of cases, transfer of the newborns from a Level III hospital (NICU) was mandatory for obstacles to offer this treatment in a NICU (hypothermia machine already in use or absence of the machine in a NICU). Every NICU should be able to perform therapeutic hypothermia and avoid transfers, which are not risk-free.

To evaluate NETS efficacy, the primary outcome was the activation time. In our study, mean activation time was shorter than 30 minutes in 93.3% of case, as international guidelines recommend. Transportation time was lower than 120 minutes only in 45.3% of case, under the standards. The explanation is that critical ill neonates as a neonate with HIE, may need longer stabilization time in birth center by the NETS team. Indeed, NETS dwell time in transferring centers, which is spent in stabilization of neonates, lasted about one hour. These data, which strongly influenced total transportation time, are necessary to understand STEN efficacy. As literature reminds us, neonatal stabilization is one of the main duties of transport services, and it affects neonatal survival outcome and overall clinical conditions[18, 19, 20].

In order to measure NETS efficacy in transferring neonates on passive cooling, we considered two parameters, body temperature (BT) and hours of live at arrival in receiving NICU.

In our sample, BT was in target range (33-35°C) in 38,5% of patients at leaving from transferring centers, and 70% of patients at final destination. Comparing these data, we highlighted a mean body temperature reduction of 0.7°C during transportation. Indeed, transportation staff was able either to preserve hypothermia in neonates already cooled either to provide a significant BT reduction during transfer when requested in a safely way considering that we did not register any case of overcooling or adverse events related to passive cooling (skin lesions).

In our work axillary temperature have been used, just because of technical impairment, for

example risk of rectal perforation using rectal thermometer in ambulance[21,22,23]. This element is significant in asphyxiated patients, with high rates of coagulopathy and possible bleeding[24, 25].

In literature, axillary temperature is reported as a validated parameter for passive cooling efficacy during transportation, and it correlates with esophageal temperature, measured at receiving NICUs[26].

In our sample, neonates arrived in the receiving NICU before the sixth hour of life in 97% of cases, while the only two patients older than six hours anyway presented a BT in therapeutically range for passive hypothermia during transportation.

CONCLUSIONS

Emergency neonatal transport service is a fundamental tool to ensure therapeutic hypothermia to eligible neonates with HIE, regardless place of birth, countries or region, such as in Campania, where there are lots of Level I centers and not all NICUs are equipped for active cooling. This work states the feasibility of passive cooling during neonatal transport with no adverse events. It also may rise the question if the use of specific mattress for neonatal therapeutic active hypothermia may improve the rate of neonates transferred with body temperature between 33 – 35°C. We believe that this could be a crucial point considering the beneficial role of therapeutic hypothermia started within 6 hours from birth of a neonate with hypoxic-ischemic encephalopathy.

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