

# Early Outcomes of Perinatal Asphyxia Management with Cool-Cap® and Blanket

## Desenlaces tempranos del manejo de la asfixia perinatal con Cool-Cap® y manta

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### ABSTRACT

**Introduction:** Short-term results obtained with body cooling using Cool-Cap® and blanket are controversial. The outcomes of the two intervention modalities are presented under the same protocol and institution. **Patients and methods:** ambidirectional cohort study of newborns with moderate or severe perinatal asphyxia treated with controlled hypothermia between 2018 and 2020 in a hospital in Bogotá, Colombia. **Results:** 164 patients received therapeutic hypothermia with the mentioned devices (Cool-Cap®: 54.2%; Manta: 45.7%). Mortality was 11.2% and 16% respectively, with a higher proportion of patients with Sarnat III in the latter group (16% vs. 6%). The Cool-Cap® group presented more cardiovascular disorders (60%); pulmonary hypertension and hematological disorders had a similar proportion in both groups. In both interventions, more than half of the patients were admitted outside therapeutic window period and had an overall mortality of 14.8% (Cool-Cap® n=7 and blanket n=7). **Conclusions:** overall mortality was 13.4%, lower than the one reported in literature, which varies between 14% and 20%, despite the fact that more than half of the patients were admitted outside the therapeutic window period. This being greater in the blanket group, a difference that is explained by the disparity in the distribution of the prognostic factors at admission of both groups.

#### Keywords

hypoxic-ischemic; asphyxia; newborn; therapeutic hypothermia; prognosis.

#### RESUMEN

**Introducción:** Los resultados a corto plazo obtenidos con el enfriamiento corporal mediante Cool-Cap® y manta son controversiales. El artículo presenta los desenlaces de las dos modalidades de intervención bajo el mismo protocolo e institución. **Pacientes y métodos:** Estudio de cohortes ambidireccional de los neonatos con asfixia perinatal, moderada o severa, tratados con hipotermia controlada entre 2018 y 2020 atendidos en un hospital en Bogotá (Colombia). **Resultados:** 164 pacientes recibieron hipotermia terapéutica con los dispositivos mencionados (Cool-Cap®: 54,2%; Manta: 45,7%). La mortalidad fue del 11,2% y del 16%, respectivamente, con una mayor proporción de pacientes con Sarnat III en este último grupo (16% vs. 6%). El grupo de Cool-Cap® presentó más trastornos cardiovasculares (60%). La hipertensión pulmonar y los trastornos hematológicos tuvieron una proporción similar en ambos grupos. En ambas intervenciones, más de la mitad de los pacientes ingresaron fuera de periodo de ventana terapéutica y tuvieron una mortalidad global del 14,8% (Cool-Cap®: n = 7; manta: n = 7). **Conclusiones:** La mortalidad global fue del 13,4%, menor a la reportada en la literatura que varía entre el 14% y el 20%, a pesar de que más de la mitad de los pacientes ingresaron fuera del periodo de ventana terapéutica. La mortalidad fue mayor en el grupo de manta, explicada por la disparidad de la distribución de los factores pronósticos al ingreso de los dos grupos.

#### Palabras clave

hipoxia-isquemia; asfixia; neonato; hipotermia terapéutica; pronóstico.

#### Introduction

Hypoxic-ischemic encephalopathy secondary to perinatal asphyxia is one of the leading causes of mortality in newborns, with a risk of death of up to 60% in cases of severe encephalopathy, and it is estimated that 40% of survivors will have some degree of disability. (1-3).

Therapeutic hypothermia has been described as an effective and safe intervention that reduces mortality and secondary disability at 18 months in patients with moderate to severe perinatal asphyxia (4). In 2013, the Cochrane group included 11 controlled studies reaffirming a reduction in mortality or major disability outcome at 18 months (RR: 0.75; 95% CI: 0.68 to 0.83), with NNT 7 (95% CI: 5-10) with the use

of therapeutic hypothermia (5). Although three systematic reviews indicated that there was no difference in efficacy between the two existing methods of therapeutic hypothermia, namely: Cool-Cap® and blanket (4-6). Studies are still lacking to determine the most appropriate method and technique for body cooling (5,7).

The controversy lies in the short-term results obtained with body cooling using the two methods since other authors mention that selective cooling by Cool-Cap® could have lower systemic effects but less effective cooling of deep brain regions (1,8-10). Additionally, Goenka et al. (11) found in a cohort that abnormalities in the extended electroencephalogram (EEG<sub>a</sub>) and brain magnetic resonance imaging (MRI) were more prevalent in selective cooling than in the group treated with total body cooling during the procedure.

There are few publications comparing the two cooling techniques. For example, Celik et al. (12) described 53 neonates with hypoxic-ischemic encephalopathy who received selective hypothermia through Cool-Cap® or total body, in whom a mortality of 6% was reported in the first group and 8% in the last mentioned.

In the study by Sarkar et al. (13), short-term and long-term outcomes were compared between the two cooling techniques with 59 neonates treated with therapeutic hypothermia, but there were no significant differences between the two techniques in terms of the need for ventilatory support (blanket: 100 % vs. Cool-Cap®: 94%; *p*: 0.49; OR: 1.9; 95% CI: 1.5-2.5), use of blood products such as platelets (blanket: 48% vs. Cool-Cap®: 58%; *p*: 0.59; OR: 0.7; 95% CI: 0.2-1.9) and fresh frozen plasma (blanket: 41% vs. Cool-Cap®: 32%; *p*: 0.58; OR: 1.4; 95% CI: 0.5-4.2) and the need for vasopressors (blanket: 59% vs. Cool-Cap®: 55%; *p*: 0.79; OR: 1.2; 95% CI: 0.4-3.4). However, this study has a small sample size and a higher incidence of mortality than that reported in other studies, probably secondary to the severity of the asphyxia.

On the other hand, the Hospital Universitario San Ignacio is part of the District Neuroprotection Network and is a reference center for perinatal asphyxia, so it attends

patients from different medical centers in Bogotá and the region, with special antenatal and perinatal conditions, such as poor prenatal care, maternal food insecurity, low socioeconomic status, difficulties in timely access to health resources, in addition to those related to delivery care, and inadequate and untimely transport (outside the window time) to our center to receive treatment, which is consistent with the difficulties reported in developing countries like Colombia (14,15). The present study describes mortality and short-term outcomes in our environment with the use of therapeutic hypothermia with Cool-Cap® (selective cooling) and blanket in the same institution during the period described.

## Methods

The project was approved by the Research and Institutional Ethics Committee of the Faculty of Medicine of the Pontificia Universidad Javeriana and the Hospital Universitario San Ignacio, which approved its development on July 31, 2020 (Act 16/2020). The information was obtained from the clinical records, so informed consent was not required.

A descriptive observational study of ambidirectional cohorts of neonates who received controlled therapeutic hypothermia protocol with Cool-Cap® or blanket with a diagnosis of moderate to severe perinatal asphyxia was carried out. All neonates attended at Hospital Universitario San Ignacio in the Newborn Unit with perinatal asphyxia who received the therapeutic hypothermia protocol with Cool-Cap® or blanket between 2018 and 2020 were included. No exclusion criteria were considered.

The electronic medical records related to hospitalization in the Newborn Unit of patients who received therapeutic hypothermia therapy were reviewed in detail, extracting data on the variables of interest. This information was recorded in REDcap by two of the researchers, and once all the records were completed, they were reviewed and cleaned to fill in missing data

and identify inconsistencies. Subsequently, the database was exported to the Microsoft Excel tool with the anonymized data, to perform the statistical analysis by intervention groups using the software's analysis tool.

The variables were analyzed as follows: quantitative variables (age at admission, gestational age, and death) were calculated with mean summary measures and standard deviation, and qualitative variables (sex, Apgar, prenatal controls, type of delivery, instrumented delivery, sentinel event, health service affiliation status, EEGa activity, seizures, limitation of therapeutic effort, time of death, respiratory disorders, hydroelectrolyte disorders, cardiovascular disorders, hematologic disorders, and renal disorders) were calculated with frequencies and proportions. There were also bivariate descriptive analyses for the study variables.

## Results

A total of 164 patients met the inclusion criteria and received controlled therapeutic hypothermia with the described devices, Cool-Cap® (54.3%) and blanket (45.7%), between 2018 and 2020. The characteristics at admission of the population are available in Table 1. Of the included patients, 159 patients were born in another institution.

**Table 1**

*Characteristics at the admission of the population related to the time of birth*

Characteristics	Cool Cap (n = 89)	Blanket (n = 75)
<b>Gestational age</b>	38.5 DE (1.4)	38.5 DE (1.3)
<b>n (%)</b>	<b>n (%)</b>	
<b>Sex</b>		
Female	25 (28.1)	21 (28.0)
Male	64 (71.9)	54 (72.0)
<b>Delivery route</b>		
Vaginal	47 (52.8)	46 (61.3)
Instrumented vaginal	10 (11.2)	11 (14.7)
Cesarean section	42 (47.2)	29 (38.7)
<b>Prenatal checkups</b>		
0 absent	6 (6.7)	9 (12.0)
1-4 deficient	44 (49.4)	26 (34.7)
More than 4 normal	39 (43.8)	40 (53.3)
Sentinel event record	54 (60.6)	48 (64.0)
<b>Apgar at 5 minutes</b>		
8-10: good condition	4 (4.7)	2 (3.0)
7-4: poor condition	66 (78.5)	55 (83.3)
3-0: severely affected	14 (16.7)	9 (13.6)
<b>Apgar at 10 minutes</b>		
8-10: good condition	30 (35.7)	23 (34.3)
7-4: poor condition	52 (61.9)	41 (61.2)
3-0: severely affected	2 (2.3)	3 (4.5)
<b>Sarnat on entry</b>		
I	42 (47.2)	33 (44.0)
II	40 (46.1)	30 (40.0)
III	6 (6.7)	12 (16.0)

A higher proportion of male newborns (72%) were found to be equally distributed in both intervention groups. There was a higher number of newborns in the Cool-Cap® group (54%) compared to the blanket (45%).

Likewise, a difference of three percentage points was found in the proportion of infants with severely affected Apgar at 10 minutes in the blanket group. Only one sentinel event was recorded in the medical record in 64.7% of extra-institutional deliveries. More than half of the patients in both groups (Cool-Cap®: 60.7% and blanket: 64%) had a documented sentinel event.

Of these, the most frequent was prolonged expulsive labor (Cool-Cap®: 21.3% and blanket: 21.3%), followed by unsatisfactory fetal status (Cool-Cap®: 14.6% and blanket: 14.7%) and

non-vigorous meconium (Cool-Cap®: 11.2% and blanket: 6.7%) (Table 2).

**Table 2**

*The main sentinel event reported in the medical record*

Sentinel event	Cool Cap® n (%)	Blanket n (%)
Prolonged expulsion	19 (21.3)	16 (21.3)
Unsatisfactory fetal status	13 (14.6)	11 (14.7)
Nonvigorous meconium	10 (11.2)	5 (6.7)
Nuchal cord	8 (8.9)	5 (6.7)
Emergency cesarean section	4 (4.5)	3 (4.0)
Abruptio placentae	4 (4.5)	1 (1.3)
Laborious extraction	2 (2.3)	1 (1.3)
Cord prolapse	1 (1.1)	1 (1.3)
Bad abdominal press	1 (1.1)	1 (1.3)
Preeclampsia or eclampsia	1 (1.1)	2 (2.7)
Uterine rupture	1 (1.1)	0
Home birth/ambulance	0	2 (2.7)
True cord knot	0	1 (1.3)
Altered Doppler ultrasound	0	1 (1.3)

In the blanket group, there was a difference of 5.3% with absent prenatal controls and 14.7% more poor prenatal controls in the blanket group. In both interventions, more than half of the patients were admitted outside the therapeutic window period (Cool-Cap®: 59% and blanket: 54.7%) (Table 3).

**Table 3**  
Characteristics at admission to the hypothermia protocol

	Cool Cap® n (%)	Blanket n (%)
<b>Protocol entry time</b>		
Less than or equal to 6 hours	36 (40.4)	34 (45.3)
More than 6 hours	53 (59.5)	41 (54.7)
<b>Extended EEG activity</b>		
Normal	41 (46.0)	31 (41.3)
Mild/abnormal	7 (7.9)	0
Moderate/abnormal	30 (33.7)	25 (33.3)
Severe/abnormal	11 (12.4)	19 (25.3)
<b>Seizures</b>	26 (29.2)	25 (33.3)

As a prognostic indicator, a 10% difference was found between patients with Sarnat III, more in the blanket than in the Cool-Cap® group. In the Cool-Cap® group, abnormal EEGa (moderately abnormal or severely abnormal) was documented in 46.1% of cases; while in the blanket group, the proportion was 58.6%.

#### Outcomes of the intervention

**Mortality.** In terms of mortality, there were 10 cases in Cool-Cap® (11.2%) and 12 in blanket (16%), with a difference between them of 4.8%.

**Mortality by prognosis.** The proportion of mortality among patients with worse prognosis (Sarnat III) was equal in both groups in this study (Cool-Cap®: n = 3 [50%] and blanket: n = 6 [50%]).

**Time of death.** The time at which this outcome occurred most frequently was after the end of the protocol, in the Cool-Cap® subgroup with Sarnat II (83.3%); while in the blanket group, it occurred during therapy in the Sarnat III subgroup (66.6%) (Table 4).

**Table 4**  
Mortality by type of therapy

Mortality	Cool-Cap® (n = 10)		Blanket (n = 12)	
	During therapy (%)	After therapy (%)	During therapy n (%)	After therapy n (%)
Sarnat I	0	1 (100)	1 (100)	0
Sarnat II	1 (16.7)	5 (83.3)	3 (60)	2 (40)
Sarnat III	1 (33.4)	2 (66.6)	4 (66.6)	2 (33.4)

**Mortality according to time of protocol entry.** The overall mortality of patients who entered the protocol at window time was 11.4 % (n = 8). In the Coolcap® group, n = 3 of 36 (8.3%), and in the blanket group, n = 5 of 34 (14.7%). For those who entered the protocol outside the therapeutic window period, mortality was 14.8%. In the Coolcap® group: n = 7 (13.2%) and in the blanket group: n = 7 (17%).

**Causes of death.** The first cause was multiple organ failure, followed by pulmonary hemorrhage, pulmonary hypertension, and disseminated intravascular coagulation (Table 5). In the blanket group, there were more patients with limitation of therapeutic effort during therapy. Eight of the 12 patients who died in the blanket group died after limitation of therapeutic effort, and three of the 10 who died in the Cool-Cap® group died after limitation of therapeutic effort.

**Table 5**  
Causes of death

Causes of death	Cool Cap® (n = 10 [%])	Blanket (n = 12 [%])
Multiple organ failure	3 (30.0)	2 (16.7)
Severe encephalopathy	1 (10.0)	3 (25.0)
Pulmonary hypertension	2 (20.0)	0 (0)
Disseminated intravascular coagulation	2 (20.0)	1 (8.3)
Intracerebral hemorrhage	0 (0)	2 (16.7)
Pulmonary hemorrhage	2 (20.0)	0 (0)
Asphyxial shock	0 (0)	2 (16.7)
Sepsis	0 (0)	1 (8.3)
Cerebral salt wasting	0 (0)	1 (8.3)



### Other intervention outcomes

Regarding clinical outcomes, 20% more cardiovascular disorders were found in the Cool-Cap® group than in the blanket group. Meanwhile, the outcome of pulmonary hypertension had a similar distribution in both groups, although almost twice as many patients with Cool-Cap® had moderate pulmonary hypertension compared to those in the blanket group (Table 6). Hematological disorders had a similar proportion in both groups (Table 6). Finally, renal disorders are the least frequent outcome in both groups; however, with a higher proportion in the blanket group (8% vs. 4.5%) (Table 6).

**Table 6**  
Early clinical outcomes

Outcomes	Cool Cap® n (%)	Blanket n (%)
<b>Cardiovascular disorders</b>	36 (60.0)	24 (40.0)
<b>Pulmonary hypertension</b>	40 (45.0)	33 (44.0)
Mild	11 (12.4)	14 (18.7)
Moderate	17 (19.1)	8 (10.7)
Severe	12 (13.5)	11 (14.7)
<b>Hypotension</b>	30 (34.0)	24 (32.0)
Mild	3 (10.0)	0 (0)
Moderate	20 (66.7)	16 (66.7)
Severe	4 (13.3)	6 (25.0)
Intractable	3 (10.0)	2 (8.3)
Arrhythmias	0 (0)	3 (4.0)
<b>Hematological disorders</b>	40 (45.0)	35 (46.0)
Increased clotting	19 (21.4)	13 (17.3)
Platelets less than 100 000	10 (11.2)	13 (17.3)
Coagulopathy	7 (7.9)	7 (9.3)
Thrombosis	2 (2.3)	1 (1.3)
Hemoconcentration	2 (2.3)	1 (1.3)
<b>Hydroelectrolytic disorders</b>		
Hypokalemia	56 (63.0)	38 (50.7)
Hypocalcemia	36 (40.5)	21 (28.0)
Hyponatremia	32 (36.0)	23 (31.8)
<b>Renal disorders</b>	4 (4.5)	6 (8.0)

### Discussion

The Hospital Universitario San Ignacio offers therapeutic hypothermia therapy for patients with perinatal asphyxia as a service to the community, free of charge. It should be clarified that it was not possible to randomize the type of intervention the patient received (Cool-Cap® or blanket), as it depended on the availability of the equipment in the institution during the study period.

This is the first report in Colombia and in the region in which the early outcomes of the two intervention modalities are presented under the same protocol and in the same institution, which guarantees standardization in the management of newborns with hypoxic-ischemic encephalopathy.

As described in other countries, there was a higher proportion of male neonates with hypoxic-ischemic encephalopathy in both groups (1,6). A high proportion of patients with a history of poor prenatal controls was found, especially in the Cool-Cap® group (26% more). This phenomenon has been identified fundamentally in the care of the migrant mother in Colombia, which has been increasing rapidly since 2018 (16). According to figures from the National Administrative Department of Statistics, they represented 0.9% of all births in 2018, while by 2020 they were 10.5% (16).

According to the cohorts studied, prolonged expulsive delivery was the most recorded event, followed by unsatisfactory fetal status, newborn with non-vigorous expulsion of meconium, and cord circling. This contrasts with that described in the literature, where the most frequent sentinel events are uterine rupture, placental abruption, cord prolapse, amniotic fluid embolism, and maternal cardiopulmonary arrest (17).

An overall mortality rate of 13.4% was documented, which is slightly lower than that reported in the literature, which varies between 14% and 20% (18). When analyzing by subgroups, 50 % of the neonates who died in the blanket group presented Sarnat III, and a significant number of these patients died during

therapeutic hypothermia therapy (66.7%). This may explain the difference in mortality between blanket and Cool-Cap® groups found in this study.

A blanket study conducted in Bogota with 64 patients reported an average onset of active hypothermia protocol of 6 hours, and the fatal outcome was associated with a longer onset time, with an overall mortality of 6.2%. However, in the report, all deaths occurred outside the therapeutic window, which represents a mortality rate in that period of 26.6% (19). In the study by Jia et al. (20), the authors described a benefit in short-term mortality for patients with moderate perinatal asphyxia between 6 and 12 hours of intervention; while in those with severe perinatal asphyxia, the benefit was only obtained in the first 6 hours of intervention.

We found that mortality in the Cool-Cap® group during the protocol was lower than that reported in the literature, while in the blanket group the values were close inside and outside the therapeutic period. The mortality described in the blanket group could be explained by the severity of the disease, which would be in agreement with Jia et al. (20).

Those patients who were admitted to the institution with Sarnat III and a severe course of the disease with progressive clinical deterioration despite interventions were presented to a multidisciplinary board (Neonatology, Neuropediatrics, Clinical Ethics Service, and Pediatric Palliative Care), where the decision was made to redirect the therapeutic effort and, in some cases, to discontinue hypothermia therapy. There are few data on end-of-life decisions in these patients, but, as in other studies, most deaths in patients with severe hypoxic-ischemic encephalopathy were preceded by end-of-life decisions (21). We consider that it is important to include them, not to attribute mortality to one or another therapy, but to the clinical condition of these patients.

Out of all patients, one-third had some type of arterial hypotension, which is lower than that reported in the literature, which can reach up to 62% (22,23). Regarding pulmonary hypertension, a significant proportion

was detected during the intervention, and mortality due to this cause was 20 % (Cool-Cap® = 8; blanket = 7). The prevalence of persistent pulmonary hypertension in patients with perinatal asphyxia varies from 13% to 25% (24). In this study, we found a similar proportion in both groups concerning severe pulmonary hypertension.

Hematological problems are the second most frequent disorders in both groups (45%), in particular increased clotting times, with an overall mortality of 31.2%, which is consistent with that described in the literature, where bleeding has a significant incidence and is also considered a predictor of mortality (25).

Other publications have reported a prevalence of acute kidney injury ranging from 11.7% to 70% (23, 26), unlike the findings of this study, where renal disorders were infrequent in both groups (6%), which is an important finding. It is worth clarifying that in the Shah et al. study (23), the patients included had dysfunction in at least one system (cardiovascular, hepatic, pulmonary or renal).

Regarding hydroelectrolytic disorders, hypocalcemia and hypokalemia were more frequent in the Cool-Cap® group, with 40.5% and 63%, respectively, than in the blanket group, with 28% and 50.7%, with a slightly higher frequency than described in previous studies (12).

Because this was an observational research of a single population, no causal conclusions were established. It did allow for the observation of outcomes during the intervention, and while generalization of the results to other contexts is limited, it contributes to the identification of clinical conditions and intervention results in the context of a high-complexity hospital in Colombia, which serves a population referred from other institutions that lack the necessary therapy and is a source of research questions regarding medium- and long-term outcomes in this population group that would require further study.

It is crucial to remember that a decisive factor in the prognosis is the adequate management of

the patient from birth, stabilization, transport, and initiation of hypothermia.

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## Conflict of interests

The authors declare that they have no conflicts of interest.

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