Thermal management with and without servo-controlled system in preterm infants immediately after birth: a multicentre, randomised controlled study

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ABSTRACT

Background The thermal servo-controlled systems are routinely used in neonatal intensive care units (NICUs) to accurately manage patient temperature, but their role during the immediate postnatal phase has not been previously assessed.

Objective To compare two modalities of thermal management (with and without the use of a servo-controlled system) immediately after birth.

Study design and setting Multicentre, unblinded, randomised trial conducted 15 Italian tertiary hospitals.

Participants Infants with estimated birth weight <1500 g and/or gestational age <30^{+6} weeks.

Intervention Thermal management with or without a thermal servo-controlled system during stabilisation in the delivery room.

Primary outcome Proportion of normothermia at NICU admission (axillary temperature 36.5°C–37.5°C).

Results At NICU admission, normothermia was achieved in 89/225 neonates (39.6%) with the thermal servo-controlled system and 95/225 neonates (42.2%) without the thermal servo-controlled system (risk ratio 0.94, 95% CI 0.75 to 1.17). Thermal servo-controlled system was associated with increased mild hypothermia (36°C–36.4°C) (risk ratio 1.48, 95% CI 1.09 to 2.01).

Conclusions In very low birthweight infants, thermal management with the servo-controlled system conferred no advantage in maintaining normothermia at NICU admission, while it was associated with increased mild hypothermia. Thermal management of preterm infants immediately after birth remains a challenge.

Trial registration number NCT03844204

What is already known on this topic?

- Hypothermia in preterm infants during the immediate postnatal phase is associated with morbidity and mortality and remains an unresolved, worldwide challenge.
- The thermal servo-controlled systems are routinely used in the neonatal intensive care unit to accurately manage patient temperature, but their role during the immediate postnatal phase has not been previously assessed.

What this study adds?

- In very low birthweight infants, thermal management with the servo-controlled system conferred no advantage in maintaining normothermia immediately after birth, while it was associated with increased mild hypothermia.
- Thermal management of preterm infants immediately after birth remains a challenge.

INTRODUCTION

Since its origins, the neonatology has recognised the maintenance of thermal homeostasis as one of the most important pillars for the care of neonates.[1 2] In newborns, optimal temperature ranges are narrow and thermoregulatory mechanisms are difficult to control, particularly in premature and low birthweight infants.[3] Hypothermia in preterm infants during the immediate postnatal phase is associated with morbidity and mortality and remains an unresolved, worldwide challenge.[4–6] Hyperthermia should also be prevented because of the U-shape relationship between admission temperature and adverse neonatal outcomes in very preterm infants.[7] Thus, current evidence suggests that, immediately after birth, every effort should be done to maintain neonatal temperature in the normal range (between 36.5°C and 37.5°C) in preterm infants.

A list of interventions has been recommended to prevent thermal loss at birth in very preterm infants, including adequate room temperature, use of infant warmers, polyethylene bags/wraps, preheated mattresses, caps and heated and humidified gases.[8–10] Unfortunately, a considerable proportion of very preterm infants are still hypothermic or hyperthermic at the time of the neonatal intensive care unit (NICU) admission.[4–7]

The thermal servo-controlled systems are routinely used in the NICU to accurately manage patient temperature, but their role during the immediate postnatal phase has not been previously

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assessed. We hypothesised that using a thermal servo-controlled system at delivery could prevent heat loss and overheating and could increase the proportion of very low birthweight infants (VLBWI) in the normal thermal range (temperature 36.5°C–37.5°C) at NICU admission.

The aim of this study was to compare two modalities of thermal management (with and without the use of a servo-controlled system) for ensuring normothermia immediately after birth in VLBWI.

METHODS

Study design

This is a multicentre, unblinded, randomised controlled trial of thermal management with or without a thermal servo-controlled system in VLBWI at birth (ClinicalTrial.gov). The trial was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained by parents or guardians.

SETTINGS

The study was conducted at 15 Italian tertiary hospitals.

PARTICIPANTS

Neonates satisfying the following inclusion criteria were eligible to participate in the study: (A) inborn, and (B) estimated birth weight <1500 g and/or gestational age $<30^{+6}$ weeks, and (C) parental consent.

Exclusion criteria were: (A) outborn, or (B) major congenital malformations (ie, cardiac disease and defects of abdominal wall) or parental refusal to participate to the study.

PROCEDURES

Detailed description of the procedures is reported in online supplemental material. After obtaining parental consent, eligible neonates were randomly assigned to either thermal management with servo-controlled system (intervention arm) or thermal management without servo-controlled system (control arm) in a 1:1 ratio according to a computer-generated, randomised sequence (simple randomisation stratified by centre). The randomised allocation was concealed.

About 10 min before delivery, the probe was positioned under the radiant warmer and set at 37°C in the intervention arm, while the radiant warmer was set at maximum output in the control arm.

All neonates allocated in both arms were put under the infant warmer and managed based on the current guidelines for neonatal resuscitation.[9 10] Each participating centre used the infant warmers already available in the delivery ward (list in online supplemental material).

In neonates allocated to the treatment group, the probe of the servo-controlled system was positioned on neonatal abdomen with an adhesive tape (after drying only the skin surface that was in contact with the probe) and set at 37°C. In neonates allocated to the control group, the radiant warmer was set to manual control with maximum output.

All other interventions were decided by the neonatal team and followed the current guidelines for neonatal resuscitation.[9 10]

At the end of the stabilisation, the probe of the servo-controlled system was removed, and the neonate was transferred to the NICU in a transport incubator (with the temperature set at 37°C).

In all participants, axillary temperature was measured with a digital thermometer (C202; Terumo, Tokyo, Japan) at the end of the stabilisation (before leaving the delivery room), at NICU admission (while the baby was still in the transport incubator), and 1 hour after NICU admission. All neonates were followed up until discharge or death.

OUTCOME MEASURES

The primary outcome measure was the proportion of neonates in the normal thermal range (temperature 36.5°C–37.5°C) at NICU admission.[11]

The secondary outcome measures included: the proportion of neonates with temperature <36.0°C at NICU admission; the proportion of neonates with mild hypothermia (36.0°C–36.4°C) at NICU admission; the proportion of neonates with temperature >38.0°C at NICU admission; the temperature at 1 hour after NICU admission; the proportion of intraventricular haemorrhage, all grades and grades III–IV); the proportion of respiratory distress syndrome; the proportion of late onset sepsis; the proportion of bronchopulmonary dysplasia (BPD); and the mortality before hospital discharge. Late-onset sepsis was defined as an infection occurring >72 hours. BPD was defined as oxygen dependency at 36 weeks' gestational age.

All predefined serious adverse events (SAE) (hypothermia <35°C; hyperthermia >39°C) were recorded.

Details about data collection are reported in online supplemental material.

MASKING

In the delivery room, healthcare givers and outcome assessors of neonatal temperature could not be masked to treatment allocation due to the characteristics of the intervention. In the NICU, healthcare givers and outcome assessors were masked to treatment allocation. The statistician who performed data analysis was masked to treatment allocation.

STATISTICAL ANALYSIS

A minimum of 248 participants (124 in each arm) was required to have a 90% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 50% to 70%. Taking into account increasing staff's attention due to trial participation and centre stratification, the final sample size was set at 450 neonates (details of sample size calculation in online supplemental material).

An interim analysis was performed on the primary endpoint and the SAEs when the first 100 participants were enrolled. Criteria for stopping for harm include: a statistically significant difference ($p<0.001$ according to the Haybittle-Peto boundary or $p<0.0294$ according to the Pocock boundary)[12] in the primary outcome between the treatment arms, or a reasonable suspected causal relationship between the intervention and SAEs. Stopping for futility and/or interim analysis for sample size adjustment were not planned.

The statistical analysis was performed as intention to treat. Categorical data were recorded as frequency and percentage, while continuous data as mean and SD. The statistical analysis included both unadjusted and adjusted analyses. Missing data were limited to some patient characteristics hence main analysis was based on complete cases.

Binary outcome measures were compared between the arms using the χ^2 test or Fisher's exact test (unadjusted analysis). Generalised mixed-effect models were estimated to measure the effect of the treatment on binary outcome measures, adjusting for centres (random effect) and unbalanced participant

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characteristics (adjusted analysis). Effect sizes were reported as relative risk (RR) with 95% CI.

Continuous outcome measures were compared between the arms using the Student's t-test (unadjusted analysis). Linear mixed-effect models were estimated to measure the effect of the treatment on continuous outcome measures, adjusting for centres (random effect) and unbalanced participant characteristics (adjusted analysis). Effect sizes were reported as mean difference (MD) with 95% CI.

The analysis of neonatal temperature at NICU admission as continuous variable was added during manuscript revision: although it was not preplanned in the study protocol, this additional analysis aimed to provide the most complete set of information to the reader.

All tests were two sided, and a p value less than 0.05 was considered statistically significant. Data were analysed using R software, V.4.0 (R Foundation for Statistical Computing, Vienna, Austria).[13]

RESULTS

Interim analysis

The interim analysis on the first 100 participants did not provide any indications for stopping for harm. Normothermia (36.5°C–37.5°C) at NICU admission was achieved in 28/50 neonates (56%) with the thermal servo-controlled system and 28/50 neonates (56%) without the thermal servo-controlled system (RR 1.00, 95% CI 0.71 to 1.41; p=0.99). No SAEs were observed.

PARTICIPANT CHARACTERISTICS

From 1 March 2019 to 29 February 2020, a total of 656 infants were screened for eligibility; of them, 206 were excluded and 450 were enrolled (figure 1). All participants received the allocated intervention; 225 neonates were allocated to the intervention arm (thermal management with a servo-controlled system) and 225 to the control arm (thermal management without a servo-controlled system). No neonates were lost to follow-up. The two arms were balanced with respect to baseline characteristics except for preeclampsia or maternal hypertension, multiple birth, umbilical cord management and respiratory management in delivery room (table 1).

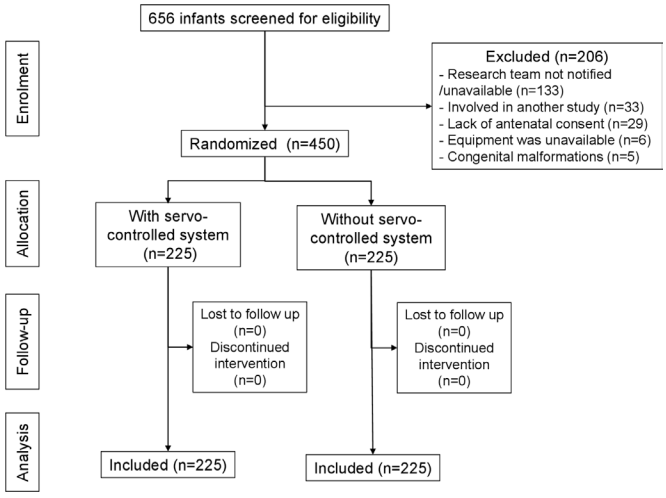

Figure 1 Enrolment and randomisation of participants.

Table 1 Participant characteristics

Participant characteristics	Thermal management with the servo-controlled system (n=225) N (%) or mean (SD) or median (IQR)	Thermal management without the servo-controlled system (n=225) N (%) or mean (SD) or median (IQR)
Maternal age, years*	34.1 (5.9)	34.6 (6.2)
Antenatal steroids:		
No	8 (3.6%)	17 (7.6%)
Incomplete cycle	35 (15.6%)	36 (16.0%)
Complete cycle	163 (72.4%)	155 (68.8%)
Not reported/unclear	19 (8.4%)	17 (7.6%)
Preeclampsia or maternal hypertension	50 (22.2%)	66 (29.3%)
Prolonged rupture of membranes >18 hours	27 (12.0%)	32 (14.2%)
IUGR	46 (20.4%)	56 (24.9%)
Multiple births	46 (20.4%)	67 (29.8%)
Maternal temperature at delivery, °C§	36.5 (0.6)	36.5 (0.5)
Caesarean section	190 (84.4%)	190 (84.4%)
Temperature of delivery/operation room, °C	24.4 (2.0)	24.4 (1.8)
Gestational age, weeks	29 (3)	29 (3)
Gestational age:		
<28 weeks	65 (28.9%)	82 (36.4%)
≥28 weeks	160 (71.1%)	143 (63.6%)
Birth weight, g	1089 (313)	1066 (327)
Birth weight		
<1000 g	90 (40.0%)	97 (43.1%)
≥1000 g	135 (60.0%)	128 (56.9%)
Males	122 (54.2%)	114 (50.7%)
5 min Apgar score^	8 (7–9)	8 (7–9)
Umbilical cord management		
Immediate cord clamping	176 (78.2%)	172 (76.4%)
Delayed cord clamping	30 (13.3%)	44 (19.6%)
Cord milking	19 (8.5%)	9 (4.0%)
Thermal interventions		
Infant warmer	225 (100.0%)	225 (100.0%)
Plastic bag-wrap	215 (95.6%)	216 (96.0%)
Hat	211 (93.8%)	216 (96.0%)
Transwarmer mattress	55 (24.4%)	50 (22.2%)
Heated humidified gases	58 (25.8%)	57 (25.3%)
Respiratory management in delivery room		
Spontaneous breathing	17 (7.5%)	19 (8.4%)
CPAP	38 (16.9%)	25 (11.1%)
Face mask ventilation	134 (59.6%)	127 (56.5%)
Intubation in delivery room	36 (16.0%)	54 (24.0%)

Data not availble in * 10, § 45 and^ 5 participants
CPAP, continuous airway positive pressure; IUGR, intrauterine growth retardation .

Primary outcome measure

At NICU admission, normothermia (36.5°C–37.5°C) was achieved in 89/225 neonates (39.6%) with the thermal servo-controlled system and 95/225 neonates (42.2%) without the thermal servo-controlled system. According to intention-to-treat analysis, the proportion of normothermic neonates was not statistically different between the arms in both unadjusted (RR 0.94, 95% CI 0.75 to 1.17) and adjusted (RR 0.89, 95% CI 0.67 to 1.14) analyses (table 2). Overall, mean neonatal temperature at NICU admission was 36.3°C (SD 0.6) with the thermal servo-controlled system and 36.5°C (SD 0.8) without the thermal servo-controlled system (MD −0.2°C, 95% CI −0.3 to −0.1°C).

Secondary outcome measures

Mild hypothermia (36°C–36.4°C) was observed at NICU admission in 74/225 neonates (32.9%) with the thermal

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Table 2 Outcome measures

Primary and secondary outcome	Outcome measure	Thermal management with the servo-controlled system (n=225)	Thermal management without the servo-controlled system (n=225)	Unadjusted analysis		Adjusted analysis*	
		N (%) or mean (SD)	N (%) or mean (SD)	RR (95% CI) or MD (95% CI)	P value	RR (95% CI) or MD (95% CI)	P value
Primary outcome measure†	Normothermia (36.5°C–37.5°C)	89 (39.6%)	95 (42.2%)	0.94 (0.75 to 1.17)	0.63	0.89 (0.67 to 1.14)	0.40
Secondary outcome measures	Moderate to severe hypothermia (<36°C)	60 (26.7%)	62 (27.6%)	0.83 (0.71 to 1.31)	0.92	0.98 (0.68 to 1.34)	0.88
	Mild hypothermia (36°C–36.4°C)	74 (32.9%)	50 (22.2%)	1.48 (1.09 to 2.01)	0.02	1.54 (1.13 to 2.01)	0.007
	Hyperthermia (>38°C)	0 (0.0%)	6 (2.7%)	0.08 (0.00 to 1.36)	0.08	–	–
	Temperature after 1 hour, °C	36.4 (0.7)	36.4 (0.8)	0.0 (-0.1 to 0.1)	0.80	0.0 (-0.1 to 0.1)	0.28
	IVH (all grades)	30 (13.3%)	33 (14.7%)	0.91 (0.57 to 1.44)	0.79	1.00 (0.60 to 1.61)	0.98
	IVH (grades III–IV)	13 (5.8%)	15 (6.7%)	0.87 (0.42 to 1.78)	0.84	–	–
	RDS	179 (79.6%)	182 (80.9%)	0.98 (0.89 to 1.07)	0.81	0.98 (0.85 to 1.07)	0.68
	Late-onset sepsis	39 (17.3%)	28 (12.4%)	1.39 (0.89 to 2.18)	0.19	1.42 (0.87 to 2.21)	0.15
	BPD	46 (20.4%)	47 (20.9%)	0.98 (0.68 to 1.41)	0.99	1.02 (0.66 to 1.50)	0.91
	Mortality	16 (7.1%)	26 (11.6%)	0.62 (0.34 to 1.12)	0.14	–	–

Two patients in the intervention arm and 12 patients in the control arm had a temperature between 37.6°C and 38°C.
*Analysis adjusted for centre, pre-eclampsia or maternal hypertension, multiple birth, umbilical cord management and respiratory management in delivery room. Regarding hyperthermia, IVH (grades III–IV) and mortality, adjusted analyses could not be performed due to the limited number of infants with the outcomes.
†In the adjusted analysis of the primary outcome, only multiple birth was associated with reduced proportion of normothermia at NICU admission (RR 0.72, 95% CI 0.49 to 0.82).
BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; RR, relative risk.

servo-controlled system and 50/225 neonates (22.2%) without the thermal servo-controlled system (unadjusted RR 1.48, 95% CI 1.09 to 2.01; adjusted RR 1.54, 95% CI 1.13 to 2.01; table 2). There was no evidence that the other secondary outcome measures differed between arms (table 2).

SAFETY

Few predefined SAEs occurred overall, with no statistically significant difference between the arms (table 3). No skin lesions due to the probe were observed.

DISCUSSION

In this multicentre trial, thermal management with the servo-controlled system conferred no advantage in maintaining normothermia immediately after birth in VLBWI. Very few adverse events occurred, and relevant clinical outcomes did not differ between arms, while mild hypothermia was more frequent among neonates managed with the servo-controlled system.

To our knowledge, this is the first trial comparing thermal management with or without servo-controlled system at birth in VLBWI. The strengths of the study include the multicentre design, the large sample size, the adoption of normothermia as primary outcome measure and the adherence to the allocation arm with no loss to follow-up. The limitations of the study include the unmasking of healthcare givers and outcome assessors in the delivery room and the lack of long-term outcomes.

A large body of literature has recognised the prognostic role of neonatal temperature immediately after birth in preterm infants.[4 7 14–17] The findings from several studies resulted in a list of recommended interventions to prevent thermal losses and highlighted the importance of avoiding hyperthermia as well as hypothermia.[7–10] To achieve such goal, this trial explored the possibility of extending to the delivery room the use of a device (the thermal servo-controlled system), which is already a standard of care in NICU. However, the findings did not support our hypothesis that using a thermal servo-controlled system at delivery could help in maintaining normothermia in VLBWI at NICU admission. We chose to set the probe at 37°C (as midpoint of normothermic range) because we were concerned about the servo-controlled system leading to hypothermia (if underset) or hyperthermia (if overset). However, given the temperature gradient between average neonatal temperature at birth of 37°C (ie, mean maternal temperature was 36.5°C and the fetus is assumed to be 0.5°C warmer than the mother) and environmental temperature of 24°C, some heat loss is expected during the first minutes of life. Hence, the probe likely signalled the infant warmer to provide maximum heat to bring the skin temperature up to the set point. We believe that this could have mitigated the impact of the servo-controlled system in maintaining normothermia, as the control arm was manually set to the maximum output. Furthermore, we found more mild hypothermia and less hyperthermia when using the servo-controlled system, which could be related to its response time in terms of increasing heater output. Unfortunately, this remains a speculation because we did not collect data on response time in our trial. Further studies may evaluate this aspect and provide insights for a more effective setting of the servo-controlled system.

Maintaining normothermia immediately after birth remains an important issue as a large proportion of preterm infants (43%–58%) is outside the normal thermal range when admitted to NICU.[4 6 7 16 18] This was confirmed in our trial, where only 4 out of 10 VLBWI were normothermic at NICU admission. Surprisingly, this proportion was lower than expected, but we believe that such finding could be explained by the large number

Table 3 Serious adverse events

Event	Thermal management with the servo-controlled system (n=225)	Thermal management without the servo-controlled system (n=225)	Unadjusted analysis	
	N (%)	N (%)	RR (95% CI)	P value
Neonatal temperature <35°C	6 (2.7)	2 (0.9)	3.00 (0.61 to 14.71)	0.28
Neonatal temperature >39°C	0 (0.0)	0 (0.0)	–	–

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of centres involved in the trial, while the expected proportion of normothermic infants was based on preliminary data from few centres during the planning of the trial.

Of note, using the thermal servo-controlled system avoided hyperthermia while it increased mild hypothermia. This is a direct effect of the patient-driven thermal management (the servo-controlled system) in comparison with the external-driven thermal management (maximum thermal power set by the healthcare giver), hence the thermal servo-controlled system may require more time to be effective in achieving normothermia. However, setting the servo-controlled system to higher temperature (ie, 37.5°C) may reduce mild hypothermia with increased risk of hyperthermia.

Of note, we chose to place the probe of the servo-controlled system on the abdomen to monitor its correct positioning and skin contact. However, we cannot exclude that different placements (ie, in the back of the infant) may lead to a different control of the temperature.

Overall, our findings strengthen the importance of efforts for improving thermal management of preterm infants immediately after birth. Despite being a reasonable hypothesis, we did not find substantial benefits of the introduction of the servo-controlled system in the delivery room. Other trials indicated positive effects of single interventions (ie, room temperature, plastic bag/wrap, preheated mattress, heated and humidified gases) in reducing neonatal hypothermia, but the proportion of preterm infants who are normothermic at NICU admission remains unsatisfactory.[8] This issue may be overcome with a comprehensive approach based on thermoregulation quality improvement initiatives, including procedures, checklists and continuous feedback to the healthcare staff.[17 19 20]

Future research may identify a comprehensive package of thermoregulation quality improvement initiatives to achieve normothermia in preterm infants immediately after birth. The inclusion of long-term assessment may quantify the impact of such initiatives. Furthermore, continuous monitoring of temperature during procedures immediately after birth could provide detailed information for thermal management.

CONCLUSIONS

In this multicentre trial, thermal management with the servo-controlled system was safe but did not improve normothermia at NICU admission in VLBWI. However, the servo-controlled system increased mild hypothermia. Thermal management of preterm infants remains a challenge that requires a comprehensive approach of thermoregulation quality improvement initiatives. Future research may investigate a suitable package of such initiatives and its impact on long-term outcomes.

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Correction notice This paper has been updated since it was published online. The affiliation of author Giulia Paviotti has been changed to Department of Neonatology, Azienda Ospedaliera Universitaria Integrata di Udine, Udine, Italy.

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SUPPLEMENTARY MATERIAL

Randomization

Eligible neonates were randomly assigned to either thermal management with servo-controlled system (intervention arm) or thermal management without servo-controlled system (control arm) in a 1:1 ratio according to a computer-generated, randomized sequence (simple randomization stratified by center). Neonates of multiple pregnancies were randomized as individuals. The randomized allocation was concealed in double-enclosed, opaque, sealed, and sequentially numbered envelopes prepared at University Hospital of Padua.

In the delivery room/operating room, the next sequential randomization envelope was opened when the neonate was considered to be eligible. The assigned procedure (with or without the servo-controlled system) was then performed. Contamination between arms was not allowed.

Description of the procedures during the trial

Written and oral information was offered to parents by the attending physician at maternal admission to the obstetrical ward or before delivery. Parents or guardians were asked to sign a written informed consent. After obtaining parental consent, all neonates with estimated birth weight <1500 g and/or gestational age $<30^{+6}$ weeks were assigned to be managed with or without the thermal servo-controlled system. Axillary maternal temperature was measured with a digital thermometer (C202; Terumo, Tokyo, Japan) about 30 minutes before delivery. About 10 minutes before delivery, the probe was positioned under the radiant warmer and set at 37°C in the intervention arm, while the radiant warmer was set at maximum output in the control arm. Room temperature was measured at the time of delivery by using a wall thermometer (Oregon Scientific RMR262) in all the study sites.

All neonates allocated in both arms were put under the infant warmer and managed based on the current guidelines for neonatal resuscitation. (9,10) Each participating center used the infant

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warmers already available in the delivery ward, including Infa Warmer i (Atom Medical USA, Wexford, PA, USA), Drager Resuscitaire Infant Warmer (Drägerwerk AG & Co., Lübeck, Germany), CosyCot™ Infant Warmer (Fisher & Paykel Healthcare Limited, Auckland, New Zealand), Panda™ Warmers, GE Healthcare, Finland, Alhena (Albano Laziale, Roma, Italy), Resuscitaire RW82VHA-1C, Hill-Rom Air-Shields (Hatboro, PA, USA). Thermoregulation interventions included the use of plastic bag and hat without drying the infant. Transwarmer mattress and/or heated humidified gases were used according to the policy of each center.

In neonates allocated to the treatment group, the probe of the servo-controlled system was positioned on neonatal abdomen with an adhesive tape (after drying only the skin surface that was in contact with the probe) and set at 37°C. Each participating center used the probe as recommended by the infant warmer manufacturer. The probe of the pulse-oximeter was positioned on the right hand or wrist in all neonates. Electrocardiogram leads were not used. In neonates allocated to the control group, the radiant warmer was set to manual control with maximum output. All other interventions, including continuous positive airway pressure (CPAP), mechanical ventilation, supplemental oxygen concentrations, administration of chest compressions and/or medications were decided by the neonatal team and followed the current guidelines for neonatal resuscitation. (9,10)

At the end of the stabilization, the probe of the servo-controlled system was removed, and the neonate was transferred to the NICU in a transport incubator (with the temperature set at 37°C).

In all participants, axillary temperature was measured with a digital thermometer (C202; Terumo, Tokyo, Japan) at the end of the stabilization (before leaving the delivery room), at NICU admission (while the baby was still in the transport incubator), and 1 hour after NICU admission. All neonates were followed up until discharge or death.

Data collection

Clinical data and maternal temperature at delivery were collected by a researcher not involved in the care of the neonates. Neonatal temperature at NICU admission and after 1 hour were collected by health care givers. All data were recorded in data sheets designed for the study and stored in password-protected computers to protect confidentiality before, during, and after the trial. Personal information was stored in a separate document accessible only by the local PI. Local anonymized datasets were shared with the study PI and then merged in the final trial dataset.

Considerations about sample size calculation

Based on unpublished observed data, we hypothesized that the proportion of neonates in the normal thermal range at NICU admission could be increased 50% to 70% by using a thermal servo-controlled system. A minimum of 248 participants (124 in each arm) was required to have a 90% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 50% to 70%. We acknowledged that participating in the trial may slightly increase staff's attention to thermal care, thus the sample size was increased to 434 neonates (217 per arm) in order to evaluate an increase from 55% in the standard of care arm to 70% in the thermal servo-controlled arm. The sample size was stratified on 15 centers, thus leading to 30 neonates per center, for a final sample size of 450 neonates.

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