Università Degli Studi Di Padova

Scuola Di Medicina E Chirurgia

Corso Di Laurea In Medicina E Chirurgia

Dipartimento Di Salute Della Donna E Del Bambino

TESI DI LAUREA

NEODRY:

EFFECT OF DRYING BEFORE PLASTIC WRAPPING ON THERMAL LOSSES IN VERY PRETERM INFANTS AT BIRTH:

A MULTICENTER, RANDOMIZED CONTROLLED TRIAL

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Anno accademico 2023/2024

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1 Abstract - Italiano

1.1.1 Presupposti dello studio

L'ipotermia nei neonati pretermine a seguito del parto è chiaramente associata a morbilità e mortalità e rimane una sfida irrisolta a livello mondiale. È raccomandata una lista di interventi, tra cui una temperatura ambientale adeguata, l'uso di termoculle, sacchetti/avvolgimenti in polietilene, materassi preriscaldati, cappellini e gas riscaldati e umidificati, per prevenire questa perdita di calore alla nascita. Tuttavia, una certa percentuale di neonati molto pretermine presenta ipotermia al momento dell'ammissione all'unità di terapia intensiva neonatale (TIN), suggerendo che siano necessarie ulteriori misure. Sebbene il procedimento di asciugatura sia raccomandato per la protezione termica dei neonati con età gestazionale superiore alle 32 settimane, questa procedura non è indicata per i neonati al di sotto della soglia, i quali dovrebbero essere inseriti in un sacchetto di polietilene immediatamente dopo la nascita senza essere asciugati. Tale indicazione si basa su studi che confrontano l'avvolgimento senza asciugatura rispetto all'asciugatura senza avvolgimento, mentre i potenziali vantaggi della combinazione di questi

interventi non sono stati esplorati. Abbiamo ipotizzato che l'asciugatura prima dell'avvolgimento in un telo di plastica potesse aiutare a prevenire la perdita di calore immediatamente dopo la nascita e ridurre l'ipotermia al momento dell'ammissione alla terapia intensiva nei neonati molto pretermine.

1.1.2 obiettivo dello studio

L'obiettivo di questo studio è stato esplorare le differenze fra due modalità di gestione termica per prevenire la perdita di calore alla nascita nei neonati molto pretermine in uno studio multicentrico, non in cieco, randomizzato e controllato che confronta l'asciugatura rispetto alla non asciugatura.

1.1.3 Materiali e metodi

Dopo aver ottenuto il consenso dei genitori, tutti i neonati con peso stimato alla nascita inferiore a 1500 g e/o età gestazionale pari o inferiore a 30+6 settimane sono stati assegnati a essere gestiti con o senza asciugatura prima della copertura con sacchetto di polietilene. La temperatura della sala parto e la temperatura materna erano misurate a circa 30 minuti prima della nascita. I pazienti assegnati a entrambi i bracci sono stati gestiti in base alle attuali linee guida per la rianimazione neonatale. L'outcome primario dello studio è stato la proporzione di neonati in normotermia (temperatura 36,5-37,5°C) al momento al ricovero in TIN. Gli outcome secondari sono stati: proporzione di neonati in ipotermia (<36,5°C e <36,0°C) ed ipertermia (temperatura >37,5°C) al momento dall'ingresso alla TIN; temperatura a 1 ora dopo il ricovero; proporzione di neonati con emorragia intraventricolare, leucomalacia periventricolare, sindrome da distress respiratorio, sepsi tardiva, displasia broncopolmonare, mortalità prima della dimissione.

1.1.4 Risultati

Complessivamente sono stati arruolati 354 pazienti. La percentuale di neonati normotermici è stata di 45.8% (81/177) nel gruppo di trattamento con asciugatura e di 46.3% (82/177) nel gruppo trattato senza asciugatura (RR 1.01, 95% CI 0.74 to 1.37).

La temperature media al ricovero era di 36.4°C (DS 0.8) nel gruppo di intervento e 36.5°C (DS 0.7) in quello di controllo (DM −0.1°C, 95% IC −0.2 to 0.1°C).

Gli outcome secondari non hanno evidenziato differenze, tranne che per l'incidenza di mortalità che è risultata significativamente più alta nei neonati trattati con asciugatura (14.7% vs 5.6%; RR 2.71, 95% CI 1.31 to 5.62).

1.1.5 Conclusioni

In conclusione, la normothermia risulta un problema rilevante nei neonati molto pretermine. Asciugare i neonati molto pretermine prima di avvolgerli in un sacchetto di polietilene alla nascita non è risultato superiore allo standard di cura (avvolgere senza asciugatura). Gli esiti clinici a breve termine erano simili tra i due bracci, ad eccezione della mortalità che è risultata significativamente più alta nel gruppo di trattamento. Questa risultato inatteso necessita di essere ulteriormente approfondito.

1.2 Abstract – English

1.2.1 Background

Hypothermia in preterm infants during the immediate postnatal phase is associated with morbidity and mortality and remains an unresolved, worldwide challenge.

A list of interventions has been recommended, including adequate room temperature, use of infant warmers, polyethylene bags/wrap, pre-heated mattresses, caps and heated and humidified gases, to prevent thermal loss at birth in very preterm infants, but a certain percentage of very preterm infants are hypothermic at the time of the neonatal intensive care unit (NICU) admission suggesting that further measures are needed. While drying is recommended for the thermal management of infants with gestational age >32 weeks, this procedure is not indicated for very preterm infants who should be put in a plastic wrap immediately at birth without drying. However, such indication is based on studies comparing wrapping without drying vs. drying without wrapping, while the potential advantages of combining these interventions were not explored. We hypothesized that drying before wrapping could prevent heat loss immediately after birth and reduce hypothermia at NICU admission in very preterm infants.

1.2.2 Aim of the study

The aim of this study was to compare two modes of thermal management (plastic wrapping with or without drying) for preventing heat loss at birth in very preterm infants in a multicentre, unblinded, randomized controlled trial that has comparing drying vs. not drying before plastic wrapping for the thermoregulation of very preterm infants at birth.

1.2.3 Materials and Methods

After obtaining parental consent, all infants with estimated birth weight <1500 g and/or gestational age ≤30+6 weeks got assigned through randomization to be managed with or without drying before plastic wrapping. Room temperature and maternal temperature were measured at the time of delivery. Patients allocated in both groups have been managed based on the current guidelines for neonatal resuscitation. The primary outcome measure will be the proportion of neonates in the normal thermal range (temperature 36.5-37.5°C) at NICU admission. Secondary outcome measures were: proportion of neonates with hypothermia (<36.5°C and <36.0°C) and hyperthermic neonates (temperature >37.5°C) at NICU admission; temperature at 1 hour after NICU admission; proportion of intraventricular hemorrhage; respiratory distress syndrome; late onset sepsis; bronchopulmonary dysplasia; incidence of mortality before hospital discharge.

1.2.4 Results

In total a number of 354 patients have been recruited. The percentage of normothermic neonates was 45.8% (81/177) in neonates treated with drying and 46.3% (82/177) in those undried (RR 1.01, 95% CI 0.74 to 1.37).

Mean neonatal temperature at NICU admission was 36.4°C (SD 0.8) in dried neonates and 36.5°C (SD 0.7) in undried neonates (MD −0.1°C, 95% CI −0.2 to 0.1°C).

There was no evidence that the other secondary outcome measures differed between the arms apart from mortality before hospital discharge that showed to be significantly higher in the group of the dried neonates (RR 2.71, 95% CI 1.31 to 5.62).

1.2.5 Conclusions

In conclusion, normothermia remains an important issue in very preterm infants. Drying very preterm infants before wrapping immediately after birth was not superior to the standard of care (wrapping without drying). Relevant clinical short-term outcomes were comparable between the two arms, except for mortality which was significantly higher in the treatment group. This unexpected finding needs to be further explored.

2 Introduction

2.1 FETAL AND NEONATAL THERMOREGULATION

2.1.1 HEAT PRODUCTION

As pregnancy unfolds a process called "heat clump", maintains the fetal temperature at 0.3-0.5°C higher than the maternal one[1], and this is relatively constant in relation to the maternal temperature variations during the day.

Many fetal metabolic processes generate heat as a by-product. The fetus's basal production is closely linked to its oxygen consumption and, therefore, fluctuates according to its oxygen needs. The heat produced within the uterus must be transferred to the mother's body for elimination. The primary pathway for heat dissipation is through the umbilical circulation, accounting for approximately 85% of fetal heat transfer.[2]; The remaining 15% is lost through the fetal skin, amniotic fluid, and uterine wall to the maternal abdomen [1].

After birth, as in all mammals, three primary mechanisms are responsible for minimizing heat loss and generating heat in cold environments: regulation of skin blood circulation through peripheral vasoconstriction, involuntary muscle activity (shivering), and thermogenesis mediated by brown adipose tissue (BAT) localized in the nape of the neck, between the scapulae, and around the kidneys and adrenal glands.

While shivering thermogenesis is the primary mechanism of heat production in adult individuals in the neonates it represents an extreme response to cold stress.

In relatively mature human newborns, it's non-shivering thermogenesis that plays the predominant role at birth. Brown fat tissue is highly innervated by sympathetic neurons. During cold stress, increased levels of noradrenaline are discharged from sympathetic nerves stimulating lipolysis in BAT, and thanks to uncoupling proteins present in the contingent mitochondria, the process is shifted towards heat dispersion. The local heat is transferred to the rest of the neonate body thanks to the rich blood supply reaching the brown fat tissue. Oxygen consumption rise 2-to-3-time folds during this response. The implication of this phenomenon hit especially the neonates that suffer from respiratory insufficiency, which is more frequent in premature or low-birth-weight neonates.

While shivering thermogenesis serves as the primary mechanism of heat generation in adults, in neonates it typically occurs as an extreme response to cold stress.

The self-regulatory thermal ability in newborn's is limited; it can tolerate a reduced environment temperature range, and it cools and heats much faster. Thermal stability gradually improves with increasing weight and maturity. To remain in a thermoneutral zone, the production of heat and its exchange with the surroundings must balance each other.

2.1.2 HEAT LOSS

At birth, the infant's temperature plummets (the expected drop in surface temperature is between 1°C and 3°C, the greatest amount of heat being lost in the first 10-20 minutes immediately after birth[3]), and a thermogenic response is evoked by the cold exposure, leading to an increase in heat production through neuroendocrine stimulation. This happens in the first few minutes of life and can continue for many hours[4]. To provide a more accurate estimate, placing a full-term, naked, wet newborn, on a cold surface immediately after birth (a table at room temperature of 25°C) can lead to a loss up to 2 degrees in core body temperature and 4 degrees in skin temperature in the first 30 minutes[5].

The intensity of the thermoregulatory responses at birth is already influenced by the route of delivery. Full-term (FT) infants born by caesarean section have temperatures on average 0.3 ° C lower than newborns delivered vaginally [6]. In the CS, the sudden exposure of the newborn's body surface to the external environment seems to create in healthy FT newborns unfavourable conditions as regards thermoregulatory adaptation compared to the progressive exposure that occurs in vaginal birth[7].

When the body surface temperature of the newborn drops immediately after birth, this is perceived by peripheral and central thermoreceptors and the signal reaches the hypothalamus (the preoptic area and the anterior hypothalamus) through afferent pathways.

Immediately after birth, the newborn's skin is covered with amniotic fluid and vernix caseosa; furthermore, the environment temperature and humidity are obviously lower than that in the uterus. The evaporation of the amniotic and fetal fluids causes a significant loss of heat in an environment with a low humidity.

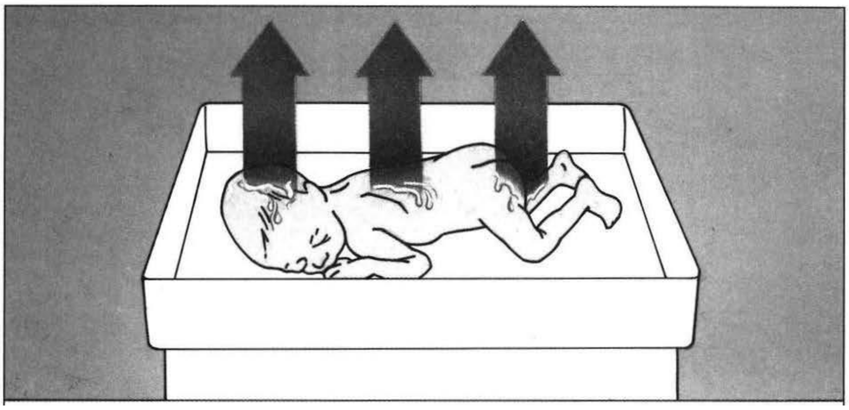

Figure 1. *Immediately after birth, the newborn loses heat by evaporation*[3].

Infants experience water loss and gain through various mechanisms. Water is lost insensibly via the respiratory tract and skin, and sensibly through urine and stool. Neonates gain water through intake from food and fluids, as well as from metabolic processes.[8–10]. In full-term infants, approximately 75% of total insensible water loss (IWL) occurs through the skin, involving the continuous diffusion of water vapor through the epidermis and from sweat gland activity.[9]. Concerning heat exchange through the respiratory tract, exhaled air is typically more humid than inhaled air, leading to greater evaporative loss when infants breathe in cold air with low water vapor pressure.

Besides evaporative heat loss, there are three additional mechanisms that contribute to reducing the newborn's body temperature.

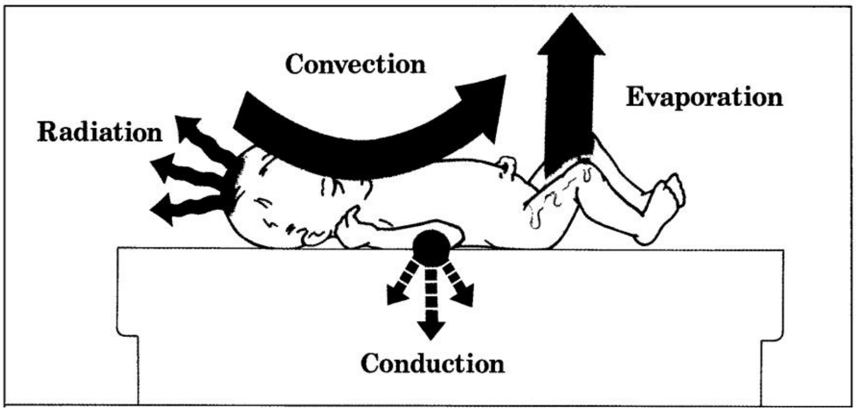

Figure 2. *Four ways a newborn may lose heat to the environment* [3].

The first mechanism of heat loss is conduction, which occurs through direct contact with cold surfaces. An infant experiences this when placed unclothed on a cold object, such as a table, weighing scale, or rubber sheet.

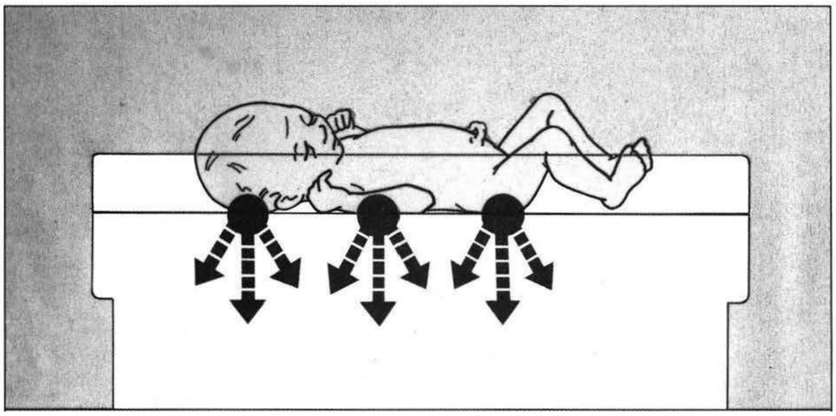

Figure 3. *A newborn will lose heat by conduction if placed naked in direct contact with a cold surface* [3].

The second mechanism is radiation, where heat is lost due to the temperature of nearby surfaces not in direct contact with the newborn. Proximity to cold walls, windows, or other objects can lead to heat loss by radiation, with the extent of loss increasing as the distance decreases and the object's temperature drops.

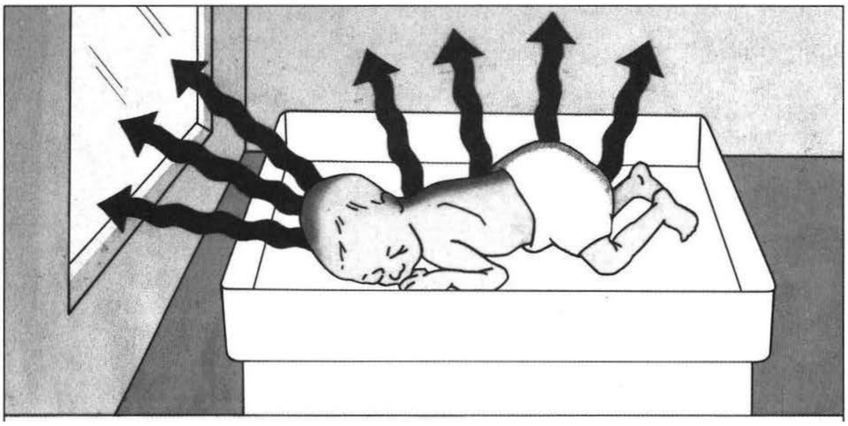

Figure 4. *A newborn will lose heat by radiation to colder surfaces such as windows and walls* [3].

The final mechanism is convection, where heat dissipates from the skin to surrounding air. This process is influenced by factors such as airflow velocity, humidity, and temperature. [10–12]. Convection heat loss occurs when a naked infant is exposed to a room temperature of 25°C, and it intensifies as the room temperature declines.

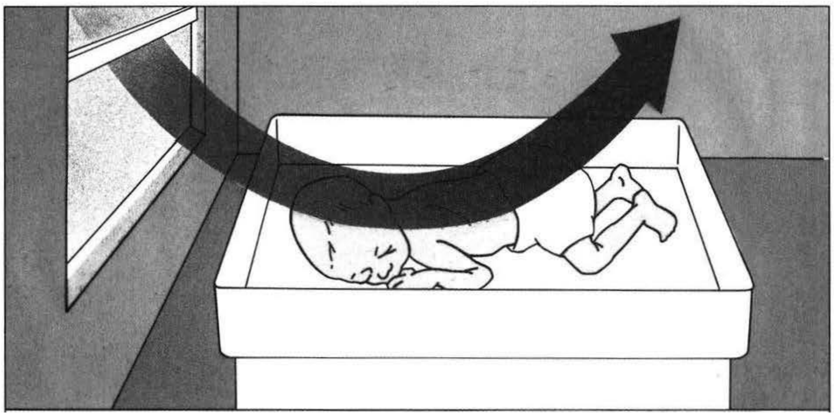

Figure 5. *Draughts, open doors or windows and air-conditioning may cause a newborn to lose heat through convection* [3].

2.1.2.1 HEAT LOSS IN PRETERM INFANTS

Preterm and low birth weight infants, characterized by epidermal immaturity are at greater risk for heat loss and dehydration. Studies[13,14] have linked Trans epidermal water loss with the degree of epidermal maturation and barrier formation in infants and observed inverse correlation with gestational age at birth and postnatal age. Epidermal immaturity creates a lack of insulative capacity through several factors: a higher ratio of skin area to weight, poor vasomotor control, high permeability of the skin (that determines a large TEWL) and reduction in subcutaneous fat, leading to hyperosmolar dehydration and thus hypothermia; furthermore, brown fat stores are less developed than those of full-term infants and glycogen stores are reduced[15], hindering heat production.

2.2 RANGE OF TEMPERATURE

2.2.1 NORMOTHERMIA

Maintaining normal thermal homeostasis at birth is one of the cornerstones for neonatal survival [16]. The WHO recommends ensuring a temperature between 36.5 and 37.5 °C to newborns (normothermic range); defining mild hypothermia as a body temperature between 36 and 36.5 °C and moderate hypothermia between 32 and 35.9 °C [3]. Severe hypothermia is defined as a temperature <32°C.

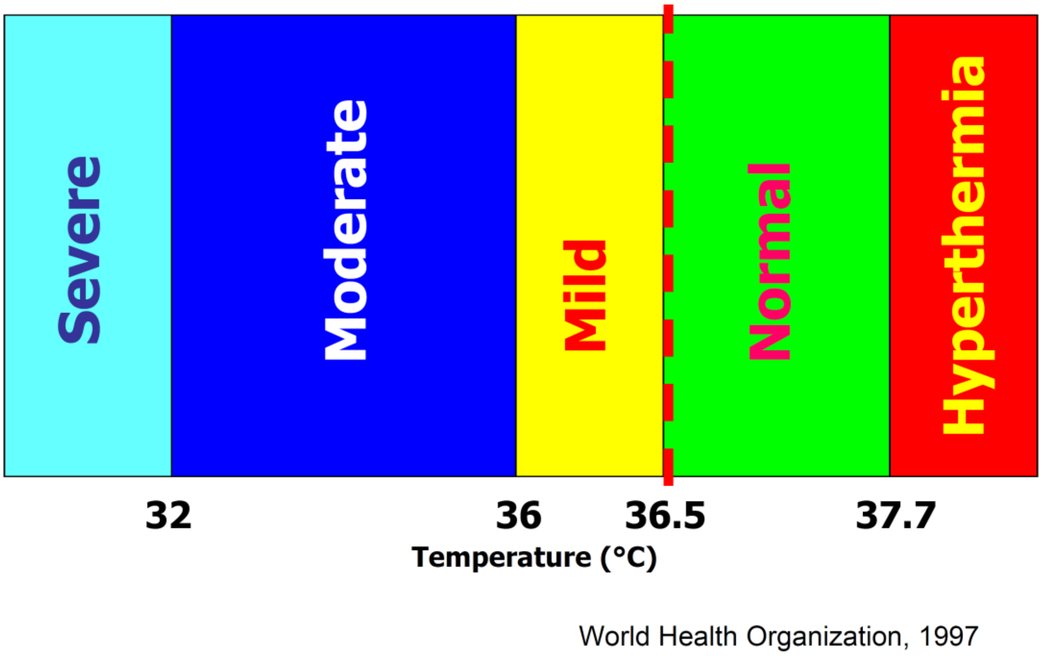

Figure 6. *Definition of thermal ranges.* [3]

Both hypothermia and hyperthermia should be avoided, due to the known U-shaped correlation between admission temperature and adverse neonatal outcomes in terms of mortality and morbidity in very preterm infants. The incidence rate of each adverse outcome within the statistical analysis reached a minimum in a specific admission temperature category[16].

If we consider the curve of estimated mortality rate associated with admission temperature, this has a similar shape in term and preterm infants, despite the latter having a higher mortality rate[17].

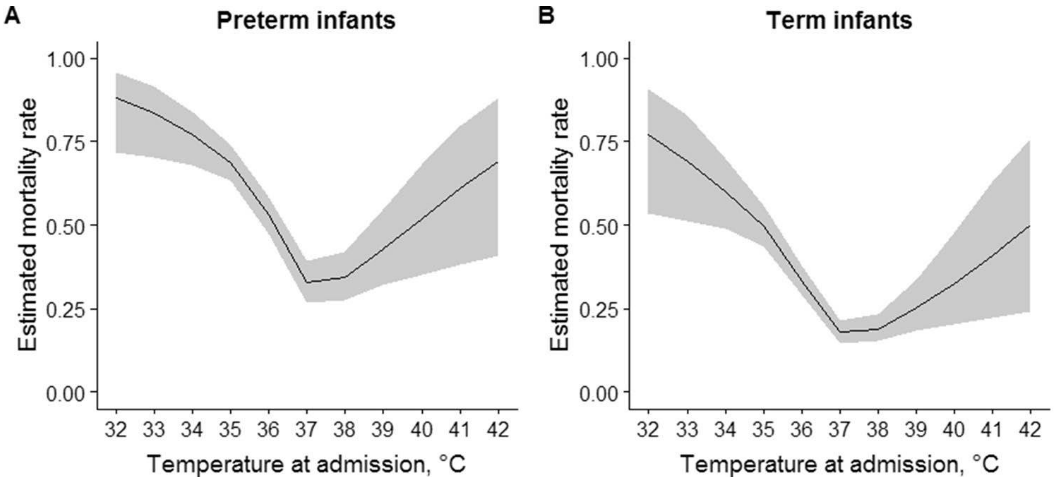

***Figure** 7. Non-linear association between mortality rate and temperature in preterm (A) and term (B) infants* [17].

2.2.2 HYPOTHERMIA

2.2.2.1 DISTRIBUTION AND RISK FACTORS

The International Consensus on cardiopulmonary resuscitation addresses hypothermia as a condition linked with numerous neonatal morbidities for both term and preterm infants[17]. Postnatal hypothermia is still reported worldwide, in both high and low resource settings, in all climates (with a higher incidence in cold seasons) and in areas with greater day-to-night thermic excursion.

In a recent randomized controlled trial conducted in the NICU of Padova, researchers evaluated the efficacy of servo-controlled versus manually controlled infant warmers. While the primary outcomes between the two groups showed no statistically significant differences, a notable finding was the incidence of hypothermia upon admission, which was observed in 40% of the infants[16].

Risk factors for the onset of hypothermia include neonatal asphyxia, prematurity and low birth weight, intrauterine growth restriction (IUGR), presence of congenital anomalies such as gastroschisis, and a damaged central nervous system[18–20].

Heat production per unit body surface area is lower in preterm infants, particularly below 28 weeks of gestation. Metabolic rates depend not only on postnatal and gestational age, but also on birth weight and size for gestation.[21–23]. Babies who are small for gestational age tend to have higher thermogenesis than gestationally immature babies of similar birth weight.[24]

Since thermogenesis requires adequate oxygenation, a distressed neonate with hypoxemia cannot produce an adequate amount of heat to increase its temperature. Furthermore, postnatal hypothermia is common in newborns born by CS[25]. The reduction in the admission temperature of newborns born by CS could be related to the lower temperature in the operating rooms, or to the use of neuraxial anaesthesia, which produces in the mother the potential for vasodilatation and a core-to-peripheral redistribution of heat through lower body sympathectomy[26,27]. Shivering, which often occurs as an adverse effect of neuraxial block, has not been shown to be effective in mitigating maternal hypothermia[28].

2.2.2.2 MEANS OF ESTIMATION OF HYPOTHERMIA

2.2.2.2.1 CLINICAL SIGNS

The typical temperature associated with cold damage in newborns is around 32.2 °C (90 °F). At these low temperatures, oxyhemoglobin remains bound and does not dissociate, causing the infants to appear very red. Because of cold injury, they may subsequently display central pallor, cyanosis, and skin changes such as edema and sclerema.

After birth, inability to nurse and suckle, weak crying, decreased activity and lethargy may be signs of hypothermia. Bradycardia and slow and irregular breathing may appear later followed by hypoglycaemia and metabolic acidosis in the last stages [29].

However, it is important to note that the clinical signs of hypothermia are not specific to hypothermia alone as they overlap with the appearance of other conditions of the newborn. These include hypoxic state, neurological depression due to hemorrhages, anemia, and generally the conditions observed in an immature infant. The overlapping symptoms can make it challenging to distinguish hypothermia from other underlying issues, necessitating thorough medical evaluation, with both machine and the clinician attention to ensure accurate diagnosis and treatment.

2.2.2.2.2 HUMAN PERCEPTION - Palpation

The WHO suggests using a combination of two-site palpation (foot and abdomen) to detect cold stress and hypothermia. However, this was not found to be reliable by studies, conducted by Ellis and co-workers and others who found that the use of touch led to underestimation of neonatal hypothermia. Furthermore, manipulation was repeatedly accounted for heat loss in literature; hence, the palpation method should be reserved for low-resource environments. In settings where thermometers are not readily available, further studies are needed to explore reliable approaches for detection through palpation as well as the application of modern on-skin technology such as the ThermoSpot device (TALC, St Albans, Hertfordshire, UK).

2.2.2.2.3 MECHANICAL SENSORS - Thermometer

Although thermal care is regarded as a crucial aspect of newborn care, the incidence of neonatal hypothermia remains high due to the lack of simple, low-cost, and acceptable tools for continuous temperature monitoring.

New methods are becoming available in high resources settings to monitor temperature, a study in 2017 measured skin temperatures in LBW infants during perioperative management using an infrared thermometry camera (Thermovision 550®). The camera was calibrated for emissivity, and infrared scans were taken every 30 seconds, digitized for analysis by two independent investigators. This non-invasive method reduces stress from skin probes and minimizes care disruptions[30].

An RCT from Indian neonatal hospital [31] was conducted in LBW newborns to study the impact of BEMPU (a hypothermia-detecting bracelet) on KMC hours at home.

Nevertheless, for the daily practice in NICU the WHO recommends the use of a low-reading mercury-in-glass thermometer, but it is fragile and difficult to obtain in many parts of the world. NICU in developed countries are usually equipped with electronic thermometer such as a Welch Allyn thermometer, which the manufacturer states have an accuracy of ±0.1 °C and its temperature range is 26.7°C–43.3 °C. Those were utilized in a recent study by G. Asefa and collaborators[32] that explored the association between temperature in the DR/OR and at the time of admission to NICU and included extremely preterm. The measurements were detected at axillary and rectal level, the latter was found to be lower with a mean difference of 0.13C°, which is less than that shown in previous reports of neonatal populations that were more mature and less likely to require NICU care[33–36] .

2.2.2.3 SHORT TERM MORBIDITY ASSOCIATED

Numerous studies report a correlation between hypothermia and coagulopathy[37], oxygen dependency, increased tendency to bleeding (particularly pulmonary hemorrhage and intraventricular hemorrhage[18]), late-onset sepsis, neurodevelopmental disturbances and respiratory disease[38–42] . Concerning the respiratory system, hypothermia plays a fundamental role, as it induces changes in the distribution of surfactant and alterations in the pulmonary circulation[41] ; as the temperature decreases, pulmonary venous vasoconstriction increases, resulting in increased pulmonary venous pressure and resistance. In addition, cold stress induces biochemical changes that may alter the infant's ability to recover from metabolic acidosis[23] .

In preterm infants with admission temperature between 36.5 and 37.2°C [26] literature shows a lower incidence of severe intraventricular haemorrhage, periventricular leukomalacia, severe retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia and nosocomial infections. A prolonged state of hypothermia can lead to impaired growth (assessed in terms of weight and height) and increased susceptibility to infections[43,44] .

2.2.2.4 PROGNOSIS

Hypothermia, regardless of gestational age or clinical setting, is linked to increased mortality and morbidity in neonates. This association suggests that a low temperature at birth may contribute to organ injury or serve as a significant marker of poor neonatal prognosis.[19,45] In accordance with the 2021 European Resuscitation Council (ERC) guidelines, it is recommended that neonatal temperature be monitored at regular intervals after birth. The temperature recorded at the time of admission to the neonatal intensive care unit (NICU) is a critical prognostic and quality indicator.[46]

In a cohort of 5,277 low birth weight infants, Laptook et al. found that for each degree of decrease in admission temperature, the odds of in-hospital mortality increased by 28%, while the odds of late-onset sepsis by 11%. [47]

More recently, Wilson et al. indicated that for each degree of temperature gained at NICU admission, mortality was lowered by 15% [48]. Furthermore, in the same study, a temperature below 35°C was associated with an increased incidence of early (first 6 days of life) and late (7 to 28 days) neonatal death[48].

2.2.3 HYPERTHERMIA

Although less common, hyperthermia can be harmful and increase the risk of neonatal mortality and morbidity[11]. The increase of temperature of the newborn is often linked to maternal hyperthermia, but it can also be due to poor management of the infant (wrapping the baby in too many blankets, excessive power settings of the infant warmer and infrequent monitoring of the temperature)[3]. Hyperthermia is referred in the ILCOR 2023[17] as a possible consequence to be wary of, especially as multiple treatment are used in the preterm infant. That said the evidences are not consistent and in recent findings[32] data was reassuring that aggressive maintenance of normothermia in the DR/OR does not increase the risk of hyperthermia.

Maternal fever during labour was found to be a proxy for neonatal fever in different studies[49–52] and was associated to adverse neonatal outcomes and cerebral palsy[49,53]. This is a reasonable assumption given the experimental evidence indicating that thermoregulation of the fetus depends on the mother. The placenta serves as the primary mechanism to dissipate 85% of the fetal heat to the maternal compartment. Consistently, one third of full-term infants born to mothers with chorioamnionitis have, 30 minutes after birth, a rectal temperature greater than 37.8 °C [49].

Hyperthermia, iatrogenic or of feverish nature, is connected to an increase in metabolic rate and loss of water by evaporation, which can lead to dehydration; This correlation remain relevant in the different birth-weight population of infants, and furthermore, a correlation emerges from literature between severe hyperthermia and perinatal respiratory depression and neurological damage, hyperthermic infants are more likely to exhibit depression at birth in the delivery room[50], and to have neurological morbidities especially seizure and cerebral palsy[51,54] but, although plausible, there is no direct evidence currently that this association is causal.

2.3 WHY AND HOW TO MAINTAIN NORMOTHERMIA?

Many interventions may be implemented to prevent heat loss and keep the infant's temperature within the normothermic range.

Despite the standard practices that constitute newborn's care immediately after birth, as wrapping in pre-warmed towels, and placement under infant warmers, the risk of hypothermia remains significant.[55].

Mechanism of heat loss	Intervention
Conduction	Skin-to-skin contact Pre-warmed resuscitation bed and linen Remove wet linen Exothermic mattress Hat/cap
Radiation	Radiant warmer
Evaporation	Plastic wrap/bag/cap Humidified heated gas
Convection	High environmental temperature Reduce air draft by closing door/window Use banks of the resuscitation bed Humidified heated gas Plastic wrap/bag/cap

Table I. Interventions to prevent neonatal hypothermia in relation to the mechanism of heat loss[11].

2.3.1 The Warm Chain

What WHO in 1997 called "warm chain" is a dated but still relevant concept, continuously evaluated and updated by professionals around the globe. It consists in a sequence of interventions aimed at minimizing heat loss. This requires training for all medical and nursing staff involved in the care of the baby and it consists of various steps, such as:

- preparing the delivery room and all the materials necessary for infant care;
- Delayed cord clamping
- drying the infant immediately after birth;
- wrapping it in warm cloths and delivering it to the mother;
- placing it on the mother's breast;
- putting a hat on the baby's head;
- covering both mother and baby;
- ensuring a warm and safe environment in case of any transport [3,56].

2.3.1.1 Environmental temperature

During the preparation of the environment, it is important that the delivery room is adequately warm, safe and free from drafts (due to open doors or windows) and from air conditioning systems. It is known that an increased ambient temperature reduces the risk of hypothermia at admission to NICU in both full-term and preterm infants [25,27,57–59].

2023 ILCOR recommendations, unchanged from 2015 over this topic, suggest a temperature of 23 to 25° in the delivery room as a strategy to avoid hypothermia in infants less than 32 weeks gestation[60]. The American Heart Association (AHA) refers to raising the room temperature above 23°C with the purpose to reduce heat loss in preterm and low-birth-weight infants or infants requiring resuscitation[60]. 2021 ERC guidelines advise to maintain the ambient temperature between 23 and 25°C for newborns between 28 and 32 gestational weeks, while increasing such cut-off above 25°C for preterm infants with gestational age less than 28 weeks[46]. According to WHO, an ideal delivery room temperature, to ensure greater maternal comfort and to avoid neonatal heat loss, should be between 25 and 28°C. There is, therefore, no consensus on the exact temperature of the delivery room, but in clinical practice, it is not easy to maintain a temperature above 25 degrees.

Regarding caesarean delivery and its specific setting, a single-centre randomized trial including 809 term and preterm infants demonstrated a lower incidence of moderate to severe hypothermia at NICU admission with an operating room temperature increased from 20 to 23°C; also, maternal hypothermia was significantly reduced.[25]

2.3.1.2 Delayed cord clamping

The World Health Organization affirms that newborns should be dried and covered before the umbilical cord is cut[3]. 2020 ILCOR guidelines state that umbilical cord clamping should be delayed in infants who do not need resuscitation, breathe or cry, have good tone and adequate heart rate; while for babies in need of resuscitation, there is not enough evidence regarding the optimum time for clamping.[60] According to 2021 ERC guidelines, options relating to the management of umbilical cord clamping should be discussed with parents prior to delivery. If neonates do not require immediate stabilization and resuscitation, clamping should be delayed for at least 60 seconds or more, if possible, as it results in a placental-newborn transfusion of circa 80 ml of whole blood (delay of three minutes leads to total transfer of 100 ml blood to the neonate).[61] Thus, where adequate thermal control and initial resuscitation steps can be ensured, it is recommended that clamping be delayed despite resuscitation procedures[46].

From the AHA 2023 guidelines[62] preterm newborn infants <34 weeks' gestation who do not require resuscitation, delaying cord clamping (≥30 seconds) can be beneficial when compared to early cord clamping (<30 seconds), and if DCC cannot be performed with babies between 28-34 weeks' gestation, intact cord milking may be reasonable. Before this gestational age (<28 weeks) intact cord milking is not recommended as in a single study severe intraventricular haemorrhage was significantly higher in those who received the cord milking compared with DCC.[63]

Some concerns remain that delayed cord clamping in the absence of adequate preventive measures may increase the risk of hypothermia[57]; if performed in a controlled environment, it does not appear to adversely affect the admission temperature and may have several benefits [64].

2.3.1.3 Hats

In the delivery room, one of the mechanisms contributing to heat loss is the loss of heat from the head. The surface of the baby's head constitutes around 20.8% of its total body surface area. Brain temperature is determined by local heat production, represented by cerebral metabolism, and its removal through the cerebral blood flow or through its dissipation from the scalp [65]. In preterm infants (<34 weeks' gestation) immediately after birth the ILCOR 2023 treatment recommendations suggests the use of a head covering to maintain normal temperature [17].

Use of woollen or cotton hats in full-term infants reduces or prevents heat loss[66] and is associated with a higher rectal temperature [67]. It is reasonable to consider the use of a plastic cap when other materials are unavailable, which was compared in trials with natural tissues hats [68].

There is currently little published evidence for preferred head coverings materials effective in preterm infants (< 34 weeks' gestation).

2.3.1.4 Skin-to-skin care

Kangaroo mother care or skin-to-skin care is an effective and easy-to-do method to promote the health of both term and preterm infants, strengthen infant-maternal bonding, encourage breastfeeding and provide thermal control; it may be associated to a lower incidence of hypothermia [69].

2023 ILCOR guidelines state that term newborns who breathe or cry, have good tone and adequate heart rate should be dried and placed on the mother's chest[17] . 2021 ERC guidelines recommend placing full-term infants and infants with gestational age greater than 32 weeks on the mother's chest and covering both with a towel.

On-going observation of preterm or low birth weight infants is required to keep their temperature within the normothermic range. Skin-to-skin care is also feasible in infants with a gestational age of less than 32 weeks, although special care is required due to the increased risk of hypothermia [46]. Per the 2023 ILCOR CoSTR, in preterm infants (<34 weeks' gestation), after birth there is insufficient published human evidence to suggest for or against the use of skin-to-skin care immediately after birth. It's a simple but effective measure that can be helpful for maintaining normothermia where few other interventions are possible. (Good practice statement). Fathers can also be involved in the procedure and help in conserving heat and avoiding hypothermia.

2.3.1.5 Drying

Wet infants exposed to room air lost nearly five times more heat than those who were dried and warmed. In vigorous infants, the simple maneuver of drying and wrapping in a warm blanket is almost as effective in diminishing heat loss as placing them under a radiant heater.[46] However, in depressed or immature infants who may be more asphyxiated or have reduced energy stores, radiant heat administered during resuscitation procedures together with plastic bags has been the key maintains body temperature while allowing access to the patient.

While drying is recommended for the thermal management of infants with gestational age >32 weeks[46,60], this procedure is not indicated for very preterm infants who should be put in a plastic wrap immediately at birth without drying, based on studies comparing wrapping without drying vs. drying without wrapping [20,70], following previous investigations on plastic wrapping which were not conducted in the delivery room environment[71,72].

However, the potential advantages of combining those interventions (drying and wrapping) were not explored. To our knowledge, only one study investigated the role of drying before wrapping in the thermal management of preterm infants, and found comparable temperatures after birth in infants wrapped after being dried and in those wrapped without drying [73].

2.3.2 In the very preterm infant.

If the newborn is below the 32 gestational weeks of age the chain tilt toward the further warming and stimulation of the infant. Strongly preterm have a high rate of unresponsiveness, the first step involves positioning on the neonatal island where an infant warmer and a thermic mattress ensure warming, with a gentle head tilt and positioning that opens the airway, the professional check for secretion and can eventually proceed with nasopharynx aspiration to clear them. Simultaneously, the neonatologist initiates tactile stimulation, gently rubbing the infant's back or flicking the soles of their feet to encourage a response.

If the infant remains unresponsive after these initial steps, the next course of action involves assessing the heart rate and breathing. Positive pressure ventilation may be administered via bag-mask ventilation to facilitate oxygenation, aiming to restore proper cardiac function and respiratory effort. Throughout this procedure, the medical team continuously monitors vital signs and employs supplemental oxygen if necessary. The use of advanced resuscitation techniques, such as chest compressions and the possible administration of medications, might also be warranted, depending on the infant's condition.

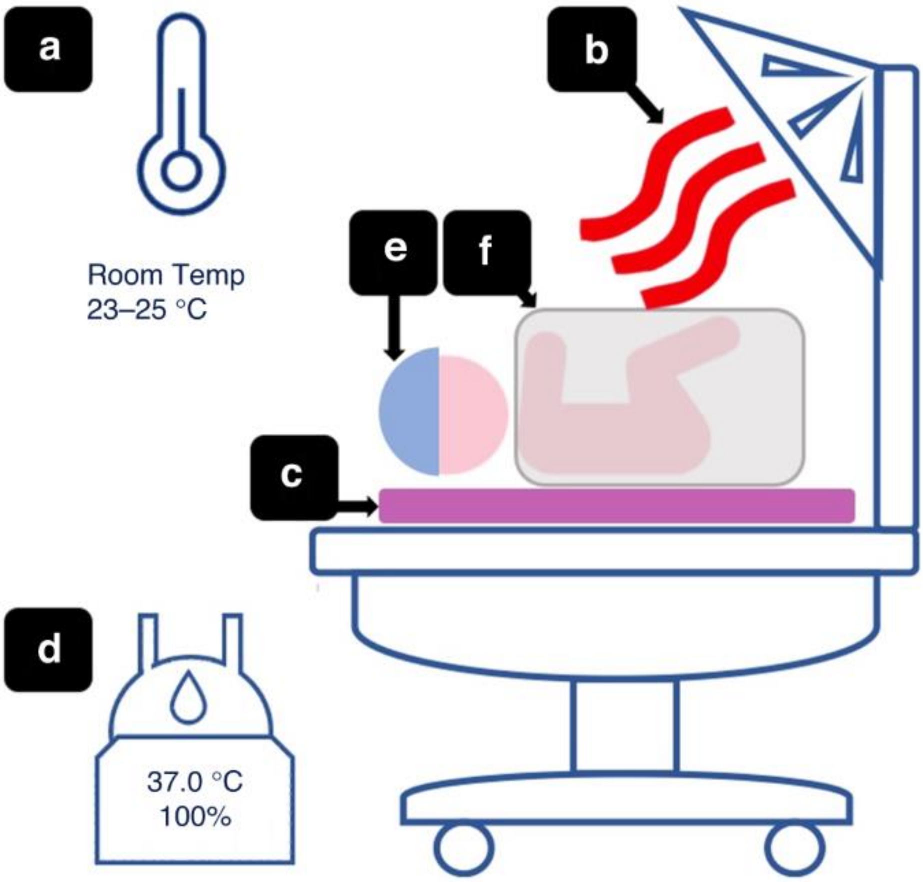

Figure 8: Thermoregulation for the very preterm newborn in the delivery room[74]: DR room temperature between 23-25 °C; b: radiant warmer; c: exothermic mattress; d: heated and humidified gases; e: woolen hat; f: polyethylene bag wrap.

2.3.2.1 Radiant warmers

After clamping the cord, infants needing further stabilization or resuscitation should be placed under the infant radiant warmer, independently of gestational age[75], as this allows thermic protection but permit direct observation, free access to the newborn and the possibility of performing any resuscitation manoeuvre.

A downside consist in a considerable variability in the power of the instrument depending on the manufacturer and, consequently, in the exposure temperature generated [11,76]. As the heat transfer is also strongly influenced by humidity and drafts in the room this complex heterogeneity potentially increases the risk of hypothermia or hyperthermia in exposed infants, [77]. To limit this variability the power should be adjusted as required, but there is insufficient evidence for or against the use of a radiant warmer in servo-controlled mode compared to manual mode for maintaining normal temperature.

In term or near-term infants with gestational age greater than 32 weeks needing support for transition or any resuscitation, 2021 ERC guidelines recommend placing the infant on a warm surface using a preheated radiant warmer. For infants with a gestational age of less than 32 weeks, they recommend placing them in polyethylene bags under the heat of a radiant source without drying (although in out-of-hospital management drying is suggested) [46].

2.3.2.2 Exothermic mattress

The mattress manages to reach a temperature between 38 and 42°C within about 90s and maintain it for up to 2 hours, thanks to the sodium acetate gel contained inside, which crystallizes exothermically when activated. The environmental temperature at which the mattress has been stored may influence its warmth[78].

Using a thermal mattress was described in one of the articles as technically easy. It might have a specific role in settings where there is a particularly high risk of hypothermia, such as for out of hospital births where other forms of thermal support such as radiant warmers are unavailable. However, no studies were found to confirm this.

The use of polyethylene bags associated with exothermic mattresses during resuscitation or transfer of very preterm infants reduces the risk of hypothermia[78,79].

Both 2020 ILCOR and 2021 ERC guidelines recommend the use of exothermic mattresses in infants born at less than 32 gestational weeks;

However, a possibility for harm was identified by 2020 American Heart Association Neonatal resuscitation guidelines, and in 2023 ILCOR. The use of these thermal mattresses has been associated with local heat injury and RR of 3.4 for hyperthermia[17,75,80].

2.3.2.3 Heated humidified gases

Supplying humidified heated gases to infants who receive respiratory support is a routine practice in the NICU and may help prevent hypothermia[80,81]. Conversely, the use of cold, dry gases during stabilization can contribute to heat loss; in fact, a 5-minute exposure of the respiratory tract to cold and dry gases may reduce lung compliance, induce the release of proinflammatory cytokines, increase work of breathing and airway resistance in preterm infants[71].

The 2020 AHA, 2021 ERC and 2023 ILCOR guidelines state that the use of warmed humidified respiratory gases in preterm infants (less than 32 weeks gestational age) receiving respiratory support should be considered.

Thermal protection should be a priority for all the subjects involved in the newborn’s care; this requires an effort to teach all health care providers and parents of infants the basic principles of thermal care. It is also necessary to implement improvement initiatives, such as staff training, assessment of the existing practice, knowledge and attitude of birth attendants, use of checklists and arrangement of teaching sessions to review both theoretical knowledge and practical skills.

2.3.2.4 Plastic bags

As premature infants have various features that predispose them to a greater loss of heat by evaporation, due to higher body surface to weight ratio and an immature epidermal barrier, the use of a polyethylene bag applied immediately after delivery reduces the impact of trans epidermal water and convective heat losses improving the admission temperature in preterm infants, especially in association with the use of an infant radiant warmer.[20] Infants must remain wrapped in the plastic bag during all resuscitation procedures.

In the Heat Loss Prevention study of infants <28 weeks' gestational age, the infants wrapped in polythene bags had a mean ± SD rectal admission temperature of 36.5 ± 0.8C.[82]

Previously a multicentre Italian study assessed whether covering the entire body with the polyethylene wrap is more effective than covering the body up to the shoulders in preventing postnatal thermal loss [83], since it was estimated that the additional coverage was approximately 15% of the total body surface. The results didn't indicate benefits of the total coverage over the partial one, that could be attributed to the presence of other interventions such as use of neonatal hats in management of the heat loss from the head.

2.3.2.4.1 Which bag?

Several types of materials are employed, including polyurethane, polyethylene, and vinyl, each offering varying degrees of insulation and durability. Vinyl bags, on the other hand, are known for their robust construction but may have different thermal efficiency. Polyurethane bags are often favoured for their lightweight nature but lack the polyethylene bags provide a balance of sturdiness and flexibility. Additionally, these bags come in single and double-layer options; double-layer bags offer enhanced insulation by creating an air pocket that further reduces heat loss, making them particularly beneficial in settings where maintaining body temperature is critical[84]. The careful selection of these bags can significantly influence the outcomes of neonatal resuscitation efforts.

The AHA recommends a combination of warming interventions to prevent the risk of hypothermia in preterm or low-birth-weight infants, including the use of plastic wraps or bags[75]. According to both ILCOR and ERC guidelines, infants less than 32 weeks gestational should be completely covered (excluding the face) with polyethylene wrapping without drying and placed under the infant warmer. A subgroup analysis by gestational age suggested that a plastic bag or wrap was more effective in preventing moderate hypothermia in high-income countries and in infants born at <28 weeks' gestation compared with those born at 28 to 33+6 weeks. [17]

2.3.3 PICOT

Within this complex picture, it was hypothesized that drying before wrapping could prevent heat loss immediately after birth and reduce hypothermia at NICU admission in very preterm infants.

No data are currently available for very preterm infants, who are at higher risk of heat loss due to evaporation.

The "PICOT" question of this study is:

- P: in very preterm infants,
- I: does drying before plastic wrapping in the delivery room,
- C: compared to standard of care (plastic wrapping without drying),
- O: increase the percentage of infants in the normal thermal range (temperature 36.5-37.5°C),
- T: at the time of admission to the NICU

3 Aims of the Study

The aim of this study is to address the long-standing issue of hypothermia and expand the evidence base on maintaining normothermia, thereby contributing to the optimization of neonatal resuscitation protocols for the most effective treatment outcomes. We aim to achieve this through the comparison of two modes of thermal management (plastic wrapping with or without drying) for preventing heat loss at birth in very preterm infants.

Primary outcome measure:

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

Secondary outcome measures:

1. Proportion of neonates with hypothermia (<36.5°C and <36.0°C) at NICU admission;
2. proportion of hyperthermic neonates (temperature >37.5°C) at NICU admission;
3. temperature at 1 hour after NICU admission;
4. proportion of intraventricular hemorrhage;
5. proportion of respiratory distress syndrome;
6. proportion of late onset sepsis;
7. proportion of bronchopulmonary dysplasia;
8. mortality before hospital discharge.

4 Materials and Methods

4.1 Study Design

This is a multicenter, unblinded, randomized controlled trial comparing drying vs. not drying before plastic wrapping for the thermoregulation of very preterm infants at birth.

This is a no-profit study. No funds have been planned for this study.

4.2 Data: Population and Settings

4.2.1 Patients and recruitment

Written and oral information was offered to parents by the attending physician at maternal admission to the obstetrical ward or before delivery. After obtaining parental consent, all infants with estimated birth weight <1500 g and/or gestational age ≤30+6 weeks were assigned to be managed with or without drying before plastic wrapping in the delivery room immediately after birth. Neonates with congenital malformations and whose parents refused consent were excluded from the study.

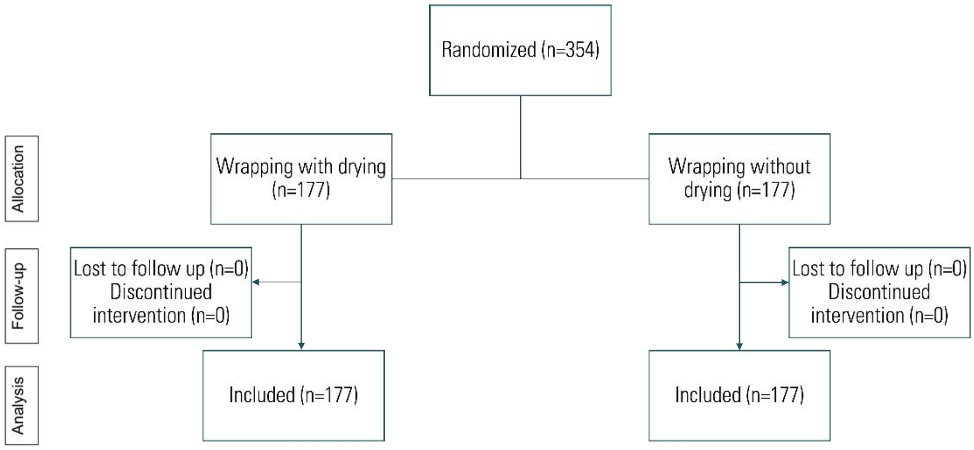

Figure 9: flowchart of randomization, allocation, follow-up and analysis

4.2.2 Sample size

We considered a number of 177 infants both for the study group and control group to be adequate since with a power of 80% and an error I type of 0.05, the minimum sample size is estimated in 346 neonates (at least 173 per arm).

4.2.3 Setting

The study was conducted at 19 level III hospitals (Department of Women's and Children's Health, Medical School, University of Padua; "San Bortolo" Hospital, Vicenza; Hospital Complex "Agostino Landolfi" Avellino; Neonatology and Intensive Care Unit, General Hospital of Bolzano; "Ca' Foncello" Hospital Treviso, "Santa Chiara" Hospital, Trento, "Burlo Garofolo" Hospital, Trieste; "Spedali Civili", "Fondazione Poliambulanza", Brescia; Policlinic G. B. Rossi - Verona; Mother and Child Department, "Mangiagalli" Major Policlinic Hospital, NICU of "Buzzi" Children Hospital, Milano; Hospital Neonatology, TINO ASO Oirm, "S. Anna", Torino; Firenze, S.O.C. Neonatology, Udine; Neonatology – Policlinic "Gemelli", Roma; NICU-Dip Interaziendale dell'eta Evolutiva – Perugia; NICU AOU Federico II – Napoli; A.O. Universitary Policlinic, Bari; NICU Ospedali Riuniti OORR, Reggio Calabria.

4.3 Intervention

Axillary maternal temperature were measured by a digital thermometer (C202; Terumo, Tokyo, Japan) about 30 minutes before delivery. Room temperature was measured at the time of delivery by using a wall thermometer (Oregon Scientific RMR262) in all the study sites.

Patients allocated in both arms have been managed based on the current guidelines for neonatal resuscitation that include the following steps:

- Maintain room temperature at least 24°C;
- Delayed cord clamping (>30 seconds) in uncompromised infants;
- Place the neonate under the radiant infant warmer with the power output set at maximum;
- Cover the body with a plastic bag/wrap up to the shoulders (with or without drying according to the randomized assignment);
- Cover the head of the baby with a cap;
- Use a pre-warmed mattress (optional);
- Use heated and humidified gases (optional).

All the other interventions, including CPAP, mechanical ventilation, supplemental oxygen concentrations, administration of chest compressions and/or medications were administered following the current guidelines for neonatal resuscitation and the decisions taken by the neonatal team.

In case of assignment to the treatment arm, the infant was be dried with a pre-warmed towel before plastic wrapping. In case of assignment to the control arm, the infant wasn't dried before plastic wrapping.

All infants were cared for in the DR with radiant warmers (PANDA i-RES; GE Healthcare, Laurel, Maryland). The warmers were turned on before birth (approximately 10 minutes before delivery) and set to manual control at 85% power output as this power value maintain a temperature exposure of approximately 40 C°. At the end of the stabilization, the patient was transferred to the NICU in a transport incubator (with the temperature set at 37°C). (PANDA i-RES; GE Healthcare, Laurel, Maryland)".

In all participants, axillary temperature was measured at 3 time points with a digital thermometer (C202; Terumo, Tokyo, Japan):

a. at the end of the stabilization (before leaving the delivery room);
b. at NICU admission (primary outcome);
c. 1 hour after NICU admission.

The study has been prolonged until the patient's discharge or death.

4.3.1 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. The statistician who performed data analysis was masked to treatment allocation.

4.4 Data

Data collected through RCP and recorded on electronic medical records started in February 2023 and ended in April 2024. We recorded the demographic data of the mother age, ethnicity, number of pregnancies, gynecological and obstetrical status with focus on blood pressure and eventual PPROM, as well as general health status. The next field was related to the delivery and regarded antenatal steroid administration, type of delivery (and reason for eventual cesarean approach), anesthesia on the mother, temperature of the mother within 30 minutes of the delivery. Regarding the infant, body characteristics such as weight, cranial circumference and length were collected along with the APGAR score at 1, 5 and 10 minutes. We collected variables of IUGR and presence of twins.

Regarding the neonatologist interventions in the delivery room we recorded the type of chord clamping (recorded as bimodal variable of immediate or delayed clamping with a cut-off of 30 seconds), presence of spontaneous respiration, need for oropharyngeal aspiration, use of positive pressure ventilation, need for mechanical external compressions, eventual intubation and drugs used for resuscitation at birth. Adding to this we collected the maximum concentration of O2 administrated to sustain blood oxygen saturation. Furthermore, we focused on the thermic care the infants received, recording the temperature in the DR at delivery, the type of Infant warmer used, and whenever the team used thermic mattresses, plastic bags, warmed and humidified gasses and hats and which material they were made.

The clinical records took note of the temperature of the neonate after birth before transfer to the neonatal intensive care unit, the use of a transport crib and its temperature setting, we recorded the time of admission to the NICU to account for the length of the transport. Once admitted the initial axillary temperature and the temperature at one hour were collected along with arterial or venous blood gases values of pH, pO2, pCO2, HCO3-, glycemia, arterial base excess, and lactates. As Ratna et al[85] proved in 2018 a good correlation and interchangeability exist from central blood gases except for values of pO2.

To account for the clinical outcomes the length of stay in the NICU and the incidence of respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), Intraventricular hemorrhage (IVH) along with its severity, periventricular leukomalacia (LMPV), necrotizing enterocolitis (NEC), and late-onset sepsis (LOS) were recorded for every patient during its permanence in the intensive care unit.

4.5 STATISTICAL ANALYSIS

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 Chi-square test or Fisher’s exact test (unadjusted analysis). Generalized mixed-effect models were estimated to measure the effect of the treatment on binary outcome measures, adjusting for the centre as random effect (adjusted analysis). Effect sizes were reported as relative risk (RR) with 95% confidence interval (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 the centre as random effect (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 4.4 (R Foundation for Statistical Computing, Vienna, Austria).

5 Results

5.1 PARTICIPANT CHARACTERISTICS

During the study period, a total of 410 infants were screened for eligibility; of them, 56 were excluded and 354 were enrolled (Figure 4). All participants received the allocated intervention; 177 neonates were allocated to the intervention arm (drying before plastic wrapping) and 177 to the control arm (not drying before plastic wrapping). No neonates were lost to follow-up. The two arms were balanced with respect to baseline characteristics (Table 2).

Table II: Patient characteristics

Participant characteristics	Drying before plastic wrapping	Not drying before plastic wrapping
	N (%) or mean (SD)	N (%) or mean (SD)
Maternal age, years [a]	34.3 (6.5)	33.1 (5.1)
Primiparous	71/175 (40.6%)	69/176 (39.2%)
Antenatal steroids:		
No	13/175 (7.4%)	9/176 (5.1%)
Incomplete cycle	15/175 (8.6%)	21/176 (11.9%)
Complete Cycle	147/175 (84.0%)	146/176 (83.0%)
IPA GRAV	42 (23.7%)	42 (23.7%)
pPROM	27 (15.3%)	19 (10.7%)
IUGR	35 (19.8%)	37 (20.9%)
Multiple births	48 (27.1%)	40 (22.6%)

Maternal temperature at delivery, °C [b]	36.5 (0.6)	36.4 (0.6)
Caesarean section	141 (79.7%)	144 (81.4%)
Temperature of delivery/operation room, °C [c]	24.2 (1.9)	24.2 (1.9)
Gestational age, weeks	28.8 (2.8)	28.5 (2.8)
Birth weight, grams	1086 (342)	1097 (307)
5 min Apgar score	8.0 (1.3)	8.0 (1.2)
Umbilical cord management:		
Immediate cord Clamping	116/175 (66.3%)	116/172 (67.4%)
Delayed cord Clamping	59/175 (33.7%)	56/172 (32.6%)
Thermal interventions:		
Infant warmer	177 (100.0%)	177 (100.0%)
Plastic bag-wrap	177 (100.0%)	177 (100.0%)
Hat	171 (96.6%)	167 (94.4%)
Transwarmer mattress	52 (29.4%)	50 (28.2%)
Heated humidified gasses	INFO DA PERUGIA	INFO DA PERUGIA
Drugs:		
Caffeine	7 (4.0%)	8 (4.5%)
Surfactant	15 (8.5%)	10 (5.6%)
Max respiratory support from delivery room to NICU:		
Spontaneous breathing	4 (2.2%)	7 (3.9%)
CPAP	121 (68.4%)	121 (68.4%)
Intubation	52 (29.4%)	49 (27.7%)
EmoGas Analysis:		
pH[d]	7.3 (0.1)	7.3 (0.1)
pCO2[d]	48.7 (12.2)	48.1 (11.6)
pO2[e]	55.9 (20.5)	53.7 (19.1)
HCO3- [f]	21.6 (3.3)	21.7 (2.83)
ABE[f]	-4.1 (4.3)	-4.0 (3.5)
Lactates, mmol/l[a]	3.8 (8.8)	3.0 (2.2)
Glycemia, mg/dl[g]	56.5 (32.0)	56.6 (29.3)

Data not available in [a]6, [b]20, [c]7, [d]1, [e]15, [f]2 and [g]16 partecipants.

5.2 PRIMARY OUTCOME

At NICU admission, normothermia (36.5°C–37.5°C) was attained in 81/177 dried neonates (45.8%) and 82/177 undried neonates (46.3%) (Image 5). According to intention-to-treat analysis, the proportion of normothermic neonates was not statistically different between the arms in both unadjusted (RR 0.99, 95% CI 0.79 to 1.24) and adjusted (RR 1.01, 95% CI 0.74 to 1.37) analyses (Table 2). Overall, mean neonatal temperature at NICU admission was 36.4°C (SD 0.8) in dried neonates and 36.5°C (SD 0.7) in undried neonates (MD −0.1°C, 95% CI −0.2 to 0.1°C).

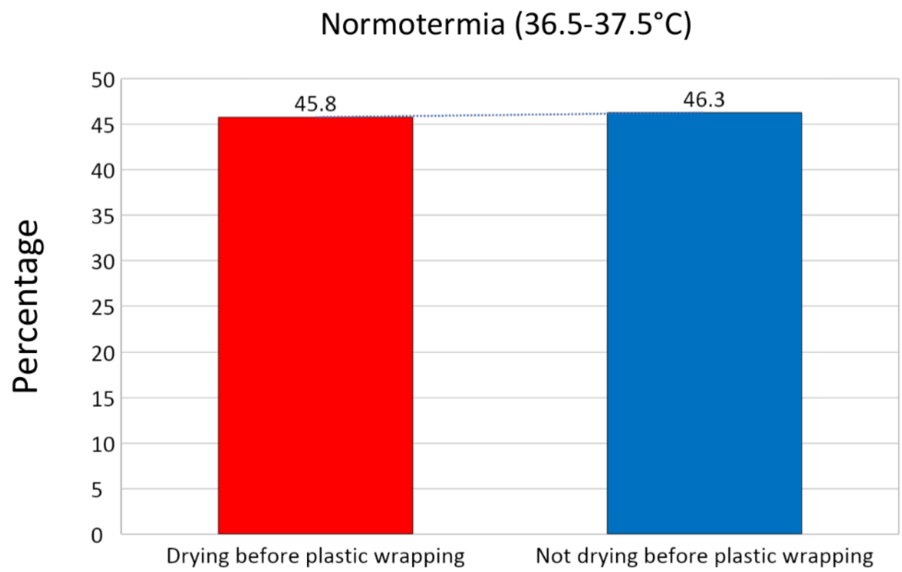

Image 10: percentage of normothermic partecipants at admission in the two grouds.

Table II: Outcome measure

Primary and secondary outcomes	*Outcome measure*	*Drying before plastic wrapping (n=177)*	*Not drying before plastic wrapping (n=177)*	*Unadjusted analysis*		*Analysis adjusted for centre*	
		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** (36.5-37.5°C)	81 (45.8%)	82 (46.3%)	0.99 (0.79 to 1.24)	0.99	1.01 (0.74 to 1.37)	0.97
Secondary outcome measure	**Hypothermia** (<36.5°C)	89 (50.3%)	81 (45.8%)	1.10 (0.88 to 0.36)	0.46	1.18 (0.88 o 1.60)	0.27
	Moderate-severe **hypothermia** (<36.0 °C)	40 (22.6%)	34 (19.2%)	1.18 (0.78 to 1.77)	0.51	1.27 (0.81 to 2.01)	0.30
	Hyperthermia (>37.5 °C)	7 (4.0%)	14 (7.9%)	0.50 (0.21 to 1.21)	0.18	0.47 (0.19 to 1.17)	0.10
	T. after 1 hour, °C	36.1 (2.6)	36.4 (0.6)	-0.3 (-0.7 to 0.1)	0.16	0.30 (-0.11 to 0.70)	0.15
	IVH (all grades)	30/175 (17.1%)	35 (19.8%)	0.87 (0.56 to 1.35)	0.62	0.86 (0.53 to 1.39)	0.53
	IVH (**III-IV grades**)	14/175 (8.0%)	14 (7.9%)	1.01 (0.50 to 2.06)	0.99	1.01 (0.48 to 2.08)	0.98
	RDS	137/176 (77.8%)	139 (78.5%)	0.99 (0.89 to 1.11)	0.98	0.97 (0.77 to 1.23)	0.81
	Late onset sepsis	32/176 (18.2%)	38 (21.5%)	0.85 (0.56 to 1.29)	0.52	0.84 (0.52 to 1.34)	0.45
	BPD	44/167 (26.3%)	52/174 (29.9%)	0.88 (0.63 to 1.24)	0.54	0.84 (0.56 to 1.26)	0.40
	Mortality	26 (14.7%)	10 (5.6%)	2.60 (1.29 to 5.23)	0.008	2.71 (1.31 to 5.62	0.007

BPD, bronchopulmonary dysplasia; CI: confidence interval; IVH, intraventricular hemorrhage; MD: mean

5.3 SECONDARY OUTCOME MEASURES

Mortality before hospital discharge was 14.7% (26/177) in dried neonates and 5.6% (10/177) in undried neonates (unadjusted RR 2.60, 95% CI 1.29 to 5.23; adjusted RR 2.71, 95% CI 1.31 to 5.62; Table 2). There was no evidence that the other secondary outcome measures differed between the arms (Table 2).

5.4 SAFETY

Few predefined SAEs occurred overall, without statistically significant difference between the two arms (Table 3).

Table III: Serious adverse events

Outcome measure	Drying before plastic wrapping (n=177)	Not Drying before plastic wrapping (n=177)	Unadjusted analysis	
	N (%)	N (%)	RR (95% CI)	p-value
Severe hypothermia (temperature <35°C)	7 (4.0%)	3 (1.7%)	2.33 (0.61 to 8.88)	0.33
Severe hyperthermia (temperature >39°C)	0 (0.0%)	0 (0.0%)	-	-

CI: confidence interval; RR, relative risk.

6 Discussion

Our results didn't show differences in temperature at admission in the NICU between the two groups, indicating no benefit from drying before wrapping preterm or VLBW newborn in polyethylene bags.

To our knowledge, this is the first trial with this numerosity comparing thermal management with or without drying before wrapping in plastic bags in VLBW and strong preterm neonates. Before this project only a small study from Cardona Torres et al[73] accounted for both drying pre-wrap and the wrapping without drying, but it only recruited 30 participants per arm, not enough to explore the implications of the intervention.

Previous studies [70,86,87] provided key data to sustain the use of plastic bag and its positive effect especially in infants of less than 28 weeks of gestational age with thermal differences up to 1.9 C° compared to the group of extremely low birth. However, the available evidence is limited to support the use of plastic in wet preterm infants at birth. So far, there has been a lack of evidence regarding the opportunity of drying these patients before covering with a plastic wrap. Drying more mature infants immediately after birth is a well-established procedure that is provided to reduce thermal losses through convection.

We hypothesized that a fast but effective drying could make the difference on the temperature curve of the newborn as it went through resuscitative measures and transport in hospital settings. This hypothesis was supported by current European Resuscitation Council Guidelines [46], that state in preterm outborn, even <32 GA, there may be benefits from placement in a food grade plastic bag after drying and with knowledge that well newborns >30 weeks gestation may be always dried before being nursed to maintain their temperature.

To confirm this uncertainty, we recruited over 350 infants to explore if clearing the infant of the residual uterine liquids with prewarmed towels could enhance the polyethylene wrap efficacy to shield off the evaporative heat loss. The drying is an intervention implemented at time zero and later the trans-epidermic loss of water continue to create superficial substrate for evaporation.

While the two groups didn’t experience statistical different incidences of hypothermia or in any other secondary outcome measured, we did have results comparable with the global admission hypothermia rate of around 50%. This means that one out of two very preterm infants is hypothermic at NICU admission suggesting it remains an important issue in this group of smaller infants. As hypothermia at NICU admission has been demonstrated to be associated with adverse outcomes, every effort should be put in place to improve this problem. Previous quality improvement studies showed that improving the rate of normothermia at NICU admission is feasible using a bundle of interventions (such as aninfant warmer, pre-warmed mattress, humidified and heated gases, woolen cap, and plastic bag) associated with the implementation of check-lists and staff debriefing.[3,11,18,88,89]

Moreover this study assessed hyperthermia incidence, which resulted to be another finding comparable to the review by McCall et al that focused on preterm infants of <37 weeks' gestation[20]. We found an hyperthermic rate slightly higher in the control group of 7.9%, while in the 12 studies reviewed by McCall the rate was around 5.4%. Our intervention group held a lower incidence of hyperthermia at 4%.

Relevant clinical short-term outcomes were comparable between the two arms, apart from mortality which was significantly higher in the treatment group (14.7%) compared to the treatment group (5.6%). As perinatal indicators, such as blood gas analyses, Apgar score at 5 minutes and resuscitation interventions, were comparable between the two arms, we don't have a specific cause able to justify this unexpected finding.

A more detailed analysis of the subgroups may help to explain this unexpected result.

The strengths of the study include its 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, and foremost the novel approach to the thermal impact of drying in the very preterm neonates.

Since the some of the thermal control means could differ between centres involved in the study, as the low evidence of benefit in the literature leave the application up to the clinicians' preferences. For this reason, the statistical analysis of the outcomes comprehended linear-mixed effects models adjustments for the random effects of centres behaviour.

Data from this study point at a subtle superior heat capacity of the watery layer still present in the wrap when applied without drying. This is not statistically significant and could be an interesting field for further studies that explore how this fluid (and other type of fluids?) interacts with the other thermoregulatory measures taken during delivery room stabilization and transport. It could be the mean by which heat from the radiant warmer better diffuse to the baby or act as a heat storage in case of fast cold exposure which otherwise activate the immature vasomotor response of the infant.

7 Conclusions

In conclusion, normothermia remains an important issue in very preterm infants. Drying very preterm infants before wrapping immediately after birth was not superior to the standard of care (wrapping without drying). Relevant clinical short-term outcomes were comparable between the two arms, except for mortality which was significantly higher in the treatment group. This unexpected finding needs to be further explored.

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