Reducing Neonatal Hypothermia in Premature Infants in an Israeli Neonatal Intensive Care Unit

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ABSTRACT **Background:** Neonatal hypothermia (< 36°C) has been associated with both neonatal morbidity and mortality.

Objectives: To develop a multifactorial approach to reduce the incidence of neonatal hypothermia at admission to the neonatal intensive care unit.

Methods: The approach involved a detailed quality improvement (QI) plan, which included the use of occlusive wrapping and exothermic mattresses as well as higher delivery and operating room environmental temperatures. The improvement plan was implemented over a 10-month period. Retrospective comparison to the same 10-month period during the previous year assessed the effectiveness of the approach in reducing the incidence of admission hypothermia.

Results: The QI project included 189 patients. These patients were compared to 180 patients during the control period. The characteristics of the patient groups were similar and included preterm infants, who were subsequently analyzed as a subgroup. We found a significant reduction in the incidence of hypothermia, which was most profound for the subgroup of premature infants born at < 32 weeks gestation. Neonatal hyperthermia was identified as an unintended consequence of the project, and subsequently improved after initiating simple preventive measures.

Conclusions: Occlusive wrapping, exothermic mattresses, and higher delivery and operating room environmental temperature may be successful in reducing admission neonatal hypothermia.

IMAJ 2020; 22: 542–546

KEY WORDS: exothermic mattress, hypothermia, neonatal, polyethylene wrap, prematurity

Neonatal hypothermia at admission to the neonatal intensive care unit (NICU) is a frequent occurrence. In very low birth weight infants, moderate hypothermia (body temperature < 36°C) is common and associated with increased mortality and morbidity [1-3]. A premature infant is particularly prone to heat loss and hypothermia due to a high surface area relative to the baby's size and the immaturity of the skin.

Each NICU has its own particular design and proximity to the labor and delivery wards and operating rooms, which may present challenges in maintaining a newly born premature infant's body temperature following delivery. At Emek Medical Center in Afula, Israel, our NICU is located in a building separate from the delivery rooms. Premature infants must be transported through an outdoor corridor exposed to the environmental temperature and weather conditions. We recognized the problem of hypothermia on admission to our unit, as 64% of our premature newborns born < 32 weeks gestation were admitted with moderate hypothermia despite the use of occlusive wrapping. We designed a quality improvement (QI) plan to improve admission temperatures and to significantly reduce the incidence of moderate hypothermia at NICU admission.

Improvement in premature newborn admission temperature has been studied and reported in the medical literature [4,5]. Strategies shown to minimize heat loss include occlusive wrapping, polyethylene caps, exothermic warming mattresses, and higher delivery room temperatures [6-10]. We proposed that a multifactorial and multidisciplinary approach would result in a reduction in the primary outcome, the incidence of moderate hypothermia (< 36°C). Secondary outcomes included mean admission temperature, mortality, the incidence of hyperthermia (≥ 37.5°C), and the incidence of sepsis. All infants admitted to our NICU were included in the project to identify systemic conditions affecting all newborns.

PATIENTS AND METHODS

This research was approved by the human research ethics committee of Emek Medical Center. Informed consent was waived.

A multidisciplinary team involving medical, nursing, and ancillary staff from neonatology, obstetrics, operating room, and anesthesiology, as well as members of the bioengineering department, designed the QI plan. The initiative progressed over 10 months and was divided into three cycles using a plan-do-study-act cycle methodology to guide the addition of interventions and to reinforce compliance. QI interventions were made prior to each of the three QI cycles in response to the analysis of baseline data and data obtained during the subsequent cycles. The first cycle occurred from 1 December 2016 to 12 February 2017, and was followed by two additional cycles (13 February 2017 to 9 June 2017 and 10 June 10 2017 to 30 September 2017). Admission temperature was obtained within 15 minutes of NICU arrival. Our unit goal was to achieve a NICU admis-

sion temperature of 36.5°C–37.5°C. Subsequent statistical analysis was designed to assess the change in the primary outcome, the incidence of hypothermia (< 36°C).

The interventions initiated prior to cycle 1:

- Bioengineering department ensured that thermostats were mounted in all operating rooms and delivery rooms, and that they were in good working order.
- An in-service education program for neonatologists, midwives, obstetricians, operating room staff, pediatric residents, and hospital staff attending newborn deliveries highlighting the need for:
  - Pre-warming of radiant warmers for all newborns
  - Pre-warming of the transport isolette
  - Increased ambient temperature in the delivery and operating rooms; the goal was 25°C
  - Occlusive wraps for all infants born < 32 weeks gestation
- Staff attending newborn deliveries were educated regarding data collection for QI. Data collection included:
  - Compliance with preheating of radiant warmers and transport isolette
  - Delivery and operating room temperature at time of delivery
  - Outdoor temperature at time of delivery
  - Compliance with use of occlusive wrap for appropriate infants

After review of the first cycle, the results of the QI project were shared and staff was reeducated. New interventions were initiated prior to the second cycle, including use of an exothermic warming mattress (TransWarmer Mattress, Model, #20421 CooperSurgical, Trumbull, CT, USA) for infants born at < 32 weeks gestation, expanded use of occlusive wrap to include infants born at 32 and 33 weeks gestation, and emphasis on wrapping of the newborn's head within the occlusive wrap (leaving the face exposed for airway management). In response to a rise in admission temperatures > 37.5°C noted in the analysis of the second cycle, the approach was changed to include the placement of a blanket between the exothermic mattress and occlusive wrap for the final QI cycle.

DATA ANALYSIS

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous variables were summarized by their means and standard deviations. To analyze the differences between the groups (newborn infants admitted to the NICU during the QI intervention and newborn infants admitted to the NICU during the same months of the preceding year and following year) in each of the categorical variables, Chi-square tests (or Fisher's exact tests when the assumptions of the parametric Chi-square test were not satisfied) were conducted. To test whether the means differed significantly in the continuous variables, Student's *t*-test (or Wilcoxon test) was performed. When comparing the 3 cycles, ANOVA testing was performed. Subgroup analysis was conducted for infants younger than 32 weeks old. Two-tailed *P* values, where $P < 0.05$ is considered statistically significant result, were conducted.

RESULTS

GENERAL DEMOGRAPHICS

The QI project included 189 consecutively born infants admitted directly from the delivery or operating room. Outborn infants transferred to our hospital and infants transferred to the NICU from the newborn nursery were excluded. Fifty infants were included during cycle 1, 67 patients for cycle 2, and 72 for cycle 3. The patient demographics and mean admission temperatures during the QI cycles were compared to the matching periods during the preceding year [Table 1].

There were no statistically significant differences in gestational age and birth weight when comparing all patients included in the QI period to those patients admitted during the year prior to the project. Mean admission temperature was significantly higher during each QI cycle than during the previous year ($P = 0.002$, $P < 0.001$, $P < 0.001$). Improvement in mean temperature was noted between QI cycle 1 and cycles 2 and 3 ($P < 0.05$). Although there was a trend to further improvement in mean admission temperature between cycle 2 and 3, this did not reach statistical significance.

There were no statistically significant differences in gestational age when comparing the subgroup of premature infants born at < 32 weeks gestation included in the QI to those patients admitted during the year prior to the project [Table 2]. Birth weight was also similar, but the premature infants who participated in cycle 1 of the QI period had a lower birth weight than those during the previous year ($P = 0.04$). Mean admission temperature was higher during the all of the QI cycles when compared to control periods of the previous year, but only reached statistical significance for the second and third cycles ($P < 0.001$, $P = 0.03$). There was also improvement in mean admission temperature between the first cycle and cycles 2 and 3 of the QI project ($P = 0.003$).

INCIDENCE OF HYPOTHERMIA

The incidence of moderate hypothermia (admission temperature of < 36°C) decreased throughout the QI project. This trend was also true for the subgroup of premature infants born at < 32 weeks gestation, those who are at greatest risk for hypothermia related morbidity [**Figure 1**].

The incidence of moderate hypothermia was lower during each QI cycle when compared with the same periods during the previous year. This improvement achieved statistical significance for all and cycles and subgroups, with the exception of cycle 2 in which a clear trend was noted that did not reach statistical significance ($P = 0.06$) for the premature infants < 32 weeks.

INCIDENCE OF HYPERTHERMIA

Changes were made to the QI project following the second cycle because of a rising incidence of hyperthermia (> 37.5°C). The increased incidence in hyperthermia was most pronounced among our subgroup of premature infants < 32 weeks. The rate of hyperthermia increased during cycle 2 (22.4%) but was followed by a reduction during the final cycle (8.3%). None of the premature infants had an admission temperature > 38°C.

AMBIENT TEMPERATURE IN DELIVERY ROOMS AND OPERATING ROOMS

As part of our QI initiative, we tracked ambient temperature in the operating rooms and delivery rooms. Compliance with recording of ambient temperature was suboptimal, reaching only 59% of patients included in the QI project. For those patients who had ambient temperature documented, low ambient temperature (< 23°C) was seen with decreasing frequency as the QI cycles progressed [Figure 2]. Outdoor temperature was similarly recorded with suboptimal compliance, and increased over the three QI cyles (11.8°C, 18.3°C, and 28.9°C) appropriate to the local seasonal weather pattern.

COMPLIANCE WITH THE QI INTERVENTIONS

We do not know the extent of compliance with the use of occlusive wraps, preheated radiant warmers, and pre-warmed transport isolettes prior to the QI project. During the study, these measures were met with full compliance. Use of exothermic mattresses was introduced during the second cycle and compliance with this intervention was excellent. All patients involved in the QI project had an admission rectal temperature taken within 15 minutes of admission.

MORBIDITY AND MORTALITY

Mortality rates were not significantly different between the control period and during the QI project: 2/178 (1.1%) vs. 3/186 (1.6%), $P = 0.692$. Similarly, the incidence of late onset neonatal sepsis was not significantly different between the groups: 4/178 (2.2%) vs. 3/186 (1.6%), $P = 0.655$.

12-MONTH FOLLOW-UP

Retrospective analysis of mean temperature and incidence of hypothermia and hyperthermia was performed for the correlating period one year after the third QI cycle to assess the continued effect of the QI project. Mean admission temperature during the third QI cycle and the correlating period during the following year were not significantly different: 36.6 ± 0.7°C and 36.4 ± 0.8°C, respectively. Similarly, the low incidence of hypothermia was maintained: 15.2% and 23% for all patients and 5.6% and 0% in premature infants < 32 weeks gestation, respectively. The overall incidence of hyperthermia remained low: 8.3% and 8.5%.

Table 1. Gestational age, birth weight, and mean temperature at admission for all patients

	Cycle 1	Cycle 2	Cycle 3
Pre-QI (2015–2016)			
N	50	65	65
Gestational age, weeks	34.4 ± 3.4	34.6 ± 3.5	33.9 ± 4
Birth weight, grams	2193 ± 752	2075 ± 723	2236 ± 739
Mean admission temperature, °C	35.8 ± 0.63	35.8 ± 0.64	36.1 ± 0.69
QI (2016–2017)			
N	50	67	72
Gestational age, weeks	33.6 ± 3.9	34.7 ± 3.7	33.9 ± 4
Birth weight, grams	1962 ± 754	2189 ± 793	2125 ± 823
Mean admission temperature, °C	36.1 ± 0.67*	36.5 ± 0.76*^	36.6 ± 0.74*^

Results are shown as mean value ± standard deviation
*$P < 0.05$ when compared to previous year
^$P < 0.05$ when compared to cycle 1
QI = quality improvement plan

Table 2. Gestational age, birth weight, and mean temperature at admission for all premature infants < 32 weeks gestational age

	Cycle 1	Cycle 2	Cycle 3
Pre-QI (2015–2016)			
N	13	14	11
Gestational age, weeks	30.5 ± 1.3	30.5 ± 3.1	30.2 ± 1.3
Birth weight, grams	1452 ± 307	1186 ± 261	1479 ± 309
Mean admission temperature, °C	35.5 ± 0.58	35.8 ± 0.61	36.1 ± 0.87
QI (2016–2017)			
N	16	14	18
Gestational age, weeks	29.0 ± 2.6	30.2 ± 3.5	28.8 ± 2.8
Birth weight, grams	1198 ± 327*	1319 ± 398	1218 ± 387
Mean admission temperature, °C	35.9 ± 0.83	37.0 ± 0.86*^	36.8 ± 0.97*^

Results are shown as mean value ± standard deviation
*P < 0.05 when compared to previous year
^P < 0.05 when compared to cycle 1
QI = quality improvement plan

Figure 1. Incidence of moderate hypothermia (< 36°C) for neonatal intensive care unit admissions

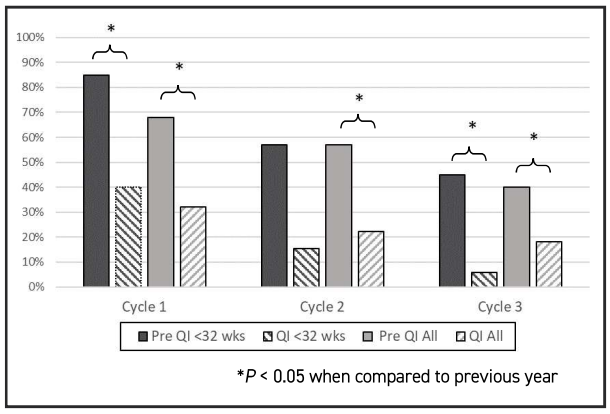
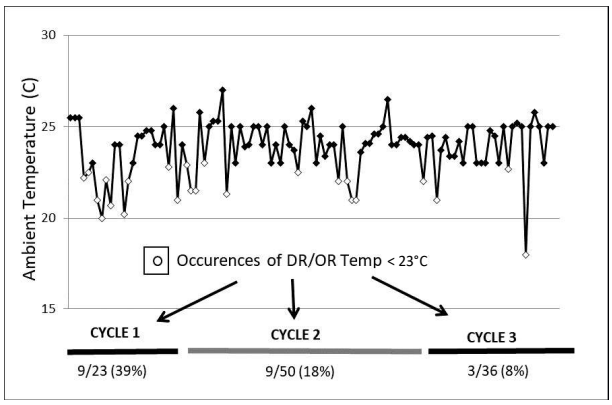


Figure 2. Delivery room/operating room ambient temperature



DISCUSSION

This QI project, designed to avoid moderate hypothermia upon NICU admission, was associated with a significant decrease in the incidence of hypothermia, our primary outcome. The greatest improvement was noted in our smallest premature infants born < 32 weeks gestation. We also noted improvement in mean admission temperature. The results are similar to those reported by Frazer et al. [4] and Russo et al. [5] who used similar QI approaches.

Kent et al. [8] also reported similar improvement, although without the use of exothermic mattresses. In our experience, improvement in admission temperature was associated with consistent use of the occlusive wrap and paralleled the increase in ambient temperature in the delivery and operating rooms during successive QI cycles. However further improvement occurred only after initiating the use of the exothermic mattress.Strict attention to environmental temperature at delivery together with the use of an occlusive wrap may not be sufficient in certain hospital settings where transport time may be prolonged and/or Strict attention to environmental temperature at delivery together with the use of an occlusive wrap may not be sufficient in certain hospital settings where transport time may be prolonged and/or there is exposure to outdoor temperatures. In these cases, the exothermic mattress may be invaluable.

We noted a concerning trend toward hyperthermia during the second cycle. Because the major change between the first two cycles was the introduction of the exothermic mattress, it seemed that the combination of occlusive wrapping and the exothermic mattress was the likely cause of the hyperthermia. A similar trend for hyperthermia with exothermic mattresses use was previously reported by McCarthy et al. [9] and Singh et al. [10]. With a small adjustment to our practice (the addition of a receiving blanket between the mattress and the wrap), this trend abated.

Of interest, we noted a trend toward improvement in mean admission temperature and reduction in admission hypothermia during the control cycle prior to the QI project. This may have been due to an increasing awareness of the problem of admission hypothermia in our unit. In addition, the first QI cycle began during the coldest time of the year with subsequent warming of the weather during the second and third cycles. Given our need to transport infants to our NICU through an outdoor corridor, the changing climate is a plausible contributor to improvement during the control cycles and during the QI project. However, the dramatic statistical improvement seen over the course of the project suggests that the QI intervention and the change in staff attitudes likely made the greatest contributions toward the improvement.

Of great importance, our QI improvement project led to a sustained change in our culture, as evidenced by persistent improvement one year following completion of the project.

LIMITATIONS

This study had some limitations. Although we saw no significant differences in mortality nor late onset sepsis, our sample size did not include enough infants to accurately report on these outcomes. In addition, our sample size and mild variation in the birth weight and gestational age between the cycles may also have contributed towards the noted improvement, as may have the seasonal weather pattern.

CONCLUSIONS

Moderate hypothermia in premature infants can be significantly reduced with a multi-disciplinary QI approach. The use of the occlusive wraps, exothermic mattresses, and ensuring a delivery/operating room environmental temperature of 23–25°C are all elements critical to success in minimizing hypothermia. Equally important is the cooperation of various departments and staff members, which can result in a culture change

emphasizing the importance of thermoregulation in newborn premature infants. It is important to emphasize that hyperthermia may arise as an unintended consequence of these interventions and should be monitored. Although improvement in neonatal admission temperature following QI initiatives has been previously reported, our medical center has unique obstacles, including the need to transport premature infants over long distances while exposed to environmental temperatures. We have shown that QI efforts aimed at improving admission temperatures can be successful despite seemingly insurmountable challenges.

ACKNOWLEDGEMENTS

The authors acknowledge Dr. Shabtai Romano, Dr. Michael Rudin, and Prof. Raed Salim, as well as our dedicated nursing staff, for their help in promoting this clinical project.

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Capsule

Phages and cancer immunity

Gut bacteria are involved in the education of T cell immune responses, and the intestinal ecosystem influences anticancer immunity. **Fluckiger** and colleagues reported microbial antigens that might cross-react with antigens associated with tumor cells. They found that a type of intestinal bacteria called enterococci harbor a bacteriophage that modulates immune responses. In mouse models, administration of enterococci containing the bacteriophage boosted T cell responses after treatment with chemotherapy or programmed cell death protein 1 (PD-1) blockade. In humans, the presence of the bacteriophage was associated with improved survival after PD-1 immunotherapy. A fraction of human T cells specific for naturally processed melanoma epitopes appeared to be able to recognize microbial peptides. This molecular mimicry may represent cross-reactivity between tumors and microbial antigens.

Science 2020; 369: 936
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Capsule

SOSTDC1 for germinal center regulation

T follicular helper (TFH) cells are CD4+ T cells that facilitate B cell antibody production and B cell memory responses in the germinal centers (GCs) of lymphoid organs. These activities are in turn restrained by T follicular regulatory (TFR) cells, a population of T cells with unclear origins. **Wu** et al. demonstrated that a subpopulation of TFH cells and fibroblastic reticular cells both produce sclerostin domain-containing protein 1 (SOSTDC1), which drove TFR cell generation by inhibiting Wnt-β-catenin signaling. In mice lacking the gene *Sostdc1*, TFR cell numbers were substantially decreased and GC responses were enhanced. These insights into TFR cell biology and GC regulation may have important implications for autoantibody-mediated diseases and the future development of vaccines and therapies for autoimmune disease.

Science 2020; 369: 984
Eitan Israeli