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Necessity of early and continuous monitoring for possible infectious complications in children undergoing therapeutic hypothermia

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Abstract

Aim: Since therapeutic hypothermia (TH) is known for its inhibitory effects on leucocyte migration and cytokine synthesis, our aim was to underline the necessity of early monitoring for potential immunomodulatory risks.

Methods: Using a 13-year retrospective case-control study at the paediatric intensive care unit (PICU) of the Medical University in Vienna, all newborn infants and children receiving TH were screened and compared with a diagnosis-matched control group undergoing conventional normothermic treatment (NT). TH was accomplished by using a non-invasive cooling device. Target temperature was 32-34°C. Children with evident infections, a medical history of an immunodeficiency or undergoing immunosuppressive therapy, were excluded.

Results: During the observational period, 108 patients were screened, 27 of which underwent TH. Culture-proven infections occurred in 22% of the TH group compared with 4% of the normothermic controls ($P = .1$). From the second day following PICU admission, median C-reactive protein (CRP) values were higher in the TH group (day two $P = .002$, day three $P = .0002$, day six $P = .008$).

Conclusion: Children undergoing TH showed earlier and higher increases in CRP levels when compared to normothermic controls. These data underline the necessity of early and continuous monitoring for possible infectious complications.

KEYWORDS

continuous monitoring, C-reactive protein, infectious complications, non-invasive cooling, therapeutic hypothermia

Abbreviations: CPR, cardiopulmonary resuscitation; CRP, C-reactive protein; IL 6, interleukin 6; NT, normothermic treatment; PICU, paediatric intensive care unit; RMSE, root mean square error; TH, therapeutic hypothermia.

1 | INTRODUCTION

Therapeutic hypothermia (TH) is an established clinical feature and treatment in critically ill newborn infants, children and adults. While TH is increasingly being integrated into daily intensive care practice, there is still a lack of data concerning its optimal use, clinical indications and side effects. The neuroprotective effects of TH; namely, reducing brain metabolism and oxygen demand,[1] have been extensively described over the past two decades. It has been shown that hypothermia hampers inflammatory cell activity by decreasing inflammatory cytokines and leukotriene production.[2,3] Mongardon et al showed an extended risk for pneumonia and bloodstream and catheter-related infections in patients undergoing TH after cardiac arrest.[4] By inhibiting proinflammatory mechanisms such as leucocyte migration, phagocytosis and proinflammatory cytokine synthesis, TH may lead to an increased risk of infection.[5] The occurrence of infections during TH, however, does not appear to worsen patient outcomes.[6-8] Mild to moderate TH (32-34°C core body temperature) rather than deep TH (<30°C) not only improves neurological outcomes, but also leads to a reduction in severe side effects.[6] TH therefore seems to be highly effective in daily clinical practice. Lin et al demonstrated improved one-month survival in children treated with TH for 72 hours. Similarly, neurological outcomes after six months were more favourable than those in normothermic patients.[9] Despite these observations, data about the use of TH in paediatrics are limited. We therefore analysed the incidence of infections and outcomes of children treated with TH (TH group) and compared them to a historical diagnosis-matched group of children as the normothermic control group (NT group).

Key Notes

- Since therapeutic hypothermia (TH) is known for its inhibitory effects on leucocyte migration and cytokine synthesis, our aim was to underline the necessity of early monitoring for potential infectious risks.
- Children undergoing TH showed earlier and higher increases in CRP levels when compared to normothermic controls.
- This single-centre analysis will help improve future management of TH in children, underlining the necessity of early and continuous monitoring for possible infectious complications.

2 | METHODS

This study was performed as a retrospective case-control study at the paediatric intensive care unit (PICU) of the Medical University of Vienna. The study was approved by the local ethics committees of our university (Ethic-Nr 1002/2012). All procedures performed were in accordance with the ethical standards of the institutional review board and with the Declaration of Helsinki. Owing to the retrospective character of this study, informed consent was waived. Patient data from 2000 to 2012 were reviewed. All medical records and laboratory files of patients, comprising newborn infants and children up to 18 years of age, receiving TH for 24-72 hours (TH group) were screened and compared to a historical normothermic control group with conventional treatment (NT group). Due to the retrospective character of this analysis and the unequally distributed groups that arose, the two groups were matched according to diagnoses. Data were analysed from the day of admission (day one) until day six, respectively, three days after completing TH. Indications for TH initiation were cardiac arrest, perinatal asphyxia, traumatic brain injury, ischemic stroke, cerebral haemorrhage and cerebral oedema or seizures, as well as acute liver failure. Infection was defined as CRP elevation above 1.2 mg/dL and/ or proven by cultures. Children with evident infection upon admission to the PICU, as well as those with a medical history of an immunodeficiency disorder or receiving immunosuppressive therapy before onset of TH were excluded from the analysis. During the observational period, parameters such as respiratory-, circulatory-, fluid-, electrolyte- nutritional- or renal management were not taken into account and were therefore not used as in- or exclusion criteria. The group undergoing mild TH (target temperature from 32 to 34°C) was induced by a non-invasive cooling device CritiCool (MTRE Advanced Technologies Ltd.). CritiCool achieves target-temperature cooling within 90 minutes, following a special algorithm based on the patient's continuous core and surface temperature to guarantee a consistently stable target temperature. For each patient age group, CritiCool offers appropriately sized cooling pads. Pads for head cooling are available for newborn infants up to school-aged children. However, specific head-cooling devices for adolescents and adults are unavailable. According to Wassink (2019) and Goenka (2019) who observed superior effects of whole-body cooling compared to selective head cooling, whole-body cooling has been performed for all ages possible.[10,11] In accordance with our institutional guidelines for carrying out TH in newborn infants, cooling was induced within the first six hours of life over a 72-hour period.[12,13] For newborn infants older than six hours, indication for hypothermia was only individually evaluated and induced for a maximum of 12 hours. During the observational period in our institution, TH was performed for 24-48 hours on children between one month and 18 years of age. Afterwards, rewarming was induced by gradually increasing the temperature from 0.2 to 0.3°C per hour. It should be emphasised that TH should only be used under strictly controlled conditions. Clinicians should be particularly vigilant about uncontrolled hyper- and/ or hypothermic events, especially in tropical climates.[14,15] All of our study patients' vital parameters, including pulsoximetry, heart rate, blood pressure, central venous pressure, core and surface temperature, were closely and continuously monitored during the entire PICU stay.

2.1 | Data protection and security

All parameters were documented in an Excel sheet (Microsoft). Patient data subject to data protection laws, such as names and addresses, were excluded from the sheet. All stored data are available only to the authors of this manuscript.

2.2 | Statistical analysis

Descriptive statistics were presented as mean and standard deviations (SD) or ranges for continuous variables, as absolute and relative frequencies for categorical variables and as median and interquartile ranges. Data collection was performed in Excel. For determining the statistical significance in categorical variables, a chi-square test and Fisher´s exact test were used, while continuous variable calculations were conducted using the Mann-Whitney *U* test, correction and two-tailed unpaired *t* test. Statistical significance was considered at a *P*-value < .05. *P*-values were not adjusted for multiple testing and should be interpreted as explorative only. The root mean square error (RMSE, R^2) was used for validation of age and CRP elevation. Survival rates were calculated using the Kaplan-Meier survival curve.

3 | RESULTS

During the observational period, a total of 108 children ranging from newborn infants to 18 years of age were included in our study. In the TH group, 55.6% of the patients were infants newborns compared with 76.5% in the NT group (*P* = .04). Due to the retrospective character of this analysis, there was a significant difference in patients' median ages at PICU admission between the TH group (0, 0/21) and NT group (0, 0/0, *P* = .02). We therefore matched according to diagnoses for both groups, comprising 27 children in the TH group and 81 children in the NT group. The matching strategy according to the primary diagnoses between both groups showed no significant differences, except for cardiac arrest (TH group, n = 12, 45% vs NT group n = 17, 21%, *P* = .02) and cerebral seizures (TH group, n = 8, 30% vs NT group n = 7, 9%, *P* = .01). Asphyxia was seen in 45% of the children in the TH group and 65% in the NT group (Figure 1). Pneumonia was the most frequent culture-proven infection found in both groups (TH n = 4, 14.8% vs NT n = 5, 6.2%, *P* = .16, Table 1). Elevation of CRP (>1.2 mg/dL) occurred in 89% of the children in the TH group, compared with 68% in the NT group during the PICU stay (*P* = .03). This CRP elevation in the TH group not only tended to be more distinctive, but also significantly higher than in the NT group from the second day following PICU admission (Figure 2). Median CRP values were at their highest in both groups on day two of admission: TH n = 26, 4.7 (2.5/7.5) mg/dL vs NT n = 81, 1.4 (0.5/4.3) mg/dL, *P* = .002. On day three, the differences in median CRP values were the most statistically significant: TH n = 22, 4.5(2.6/7.7) mg/dL vs NT n = 80, 1(0.3/3.3) mg/dL, *P* = .0002. On day six, elevations in median CRP values only occurred in the TH group: TH n = 23, 2.1 (1.4/5.4) mg/dL vs NT n = 67, 1(0.5/2.8) mg/dL, *P* = .008. There was no difference between CRP values on day two, three or six between neonates and all children older than one month, independent if they underwent TH or not (day two *P* = .253; day three *P* = .234; day six *P* = .241). Also, on the basis of a linear regression of age and the extent of CRP elevation following from the second day following after admission to the PICU RSME remained low (day two R^2 = .183, day three R^2 = .926, day six R^2 = .111). Analyses of various coagulation parameters showed no significant difference between the two groups (Table 2). Overall, no differences in survival rates were found: 81% in the TH group vs 78% in NT group, *P* = .99 (Figure 3). Furthermore, length of PICU stay was not statistically significant either: 13 (9/21) days in the TH group 13 (9/21) days vs 12 (9/23) days in the NT group, *P* = .87.

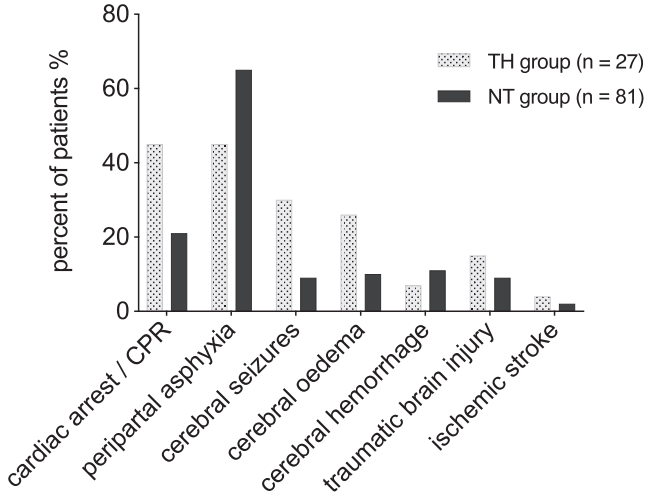

FIGURE 1 Primary diagnoses. Data are presented as percentages unless otherwise indicated

4 | DISCUSSION

This study found that the incidence of CRP elevation in TH-treated children was higher than in NT patients. Despite the prophylactic use of antibiotics at the PICU, newborn infants and children in the TH group of this analysis had significantly elevated CRP values, potentially owing to infections. In the TH group, elevated CRP levels occurred earlier and were more pronounced than within the NT group. In both groups, the most common culture-proven infection was pneumonia. As stated by Kimura et al, moderate TH can induce proinflammatory mechanisms.[2] However, in most cases, inflammation parameters were elevated without finding the source of infection. In our analysis, we also observed a higher and prolonged onset of CRP elevation during TH and have stated a lack of proven infections. Therefore, since it remains unclear what the CRP rises are resulting from, this analysis underlines the need for stringent monitoring for potential secondary infectious complications in patients undergoing TH. It should be emphasised that Geurts et al described an association between TH and a higher risk of sepsis, however,

TABLE 1 Types of infections during PICU stay and pathogen

	Pathogen (n)	
Type of infection	**TH group**	**NT group**
Pneumonia	*Candida albicans* (2) Rhinovirus (1) *Streptococcus pneumoniae* (1)	*Beta-hemolyt. streptococ.* (1) unknown (4)
Encephalitis	Enterovirus (1)	None
Gastroenteritis	*Clostridium difficile* (1)	None
Sepsis	None	Unknown (1)
Peritonitis	None	Anaerobic (1)
Eye infection	None	*Escherichia coli*, *Staphylococcus aureus* (1)
Skin infection	None	*Escherichia coli*, *Staphylococcus aureus*, Staphylococ. coag. neg., *Klebsiella pneumoniae* (1)

Note: Data are presented as numbers (n) unless otherwise indicated.

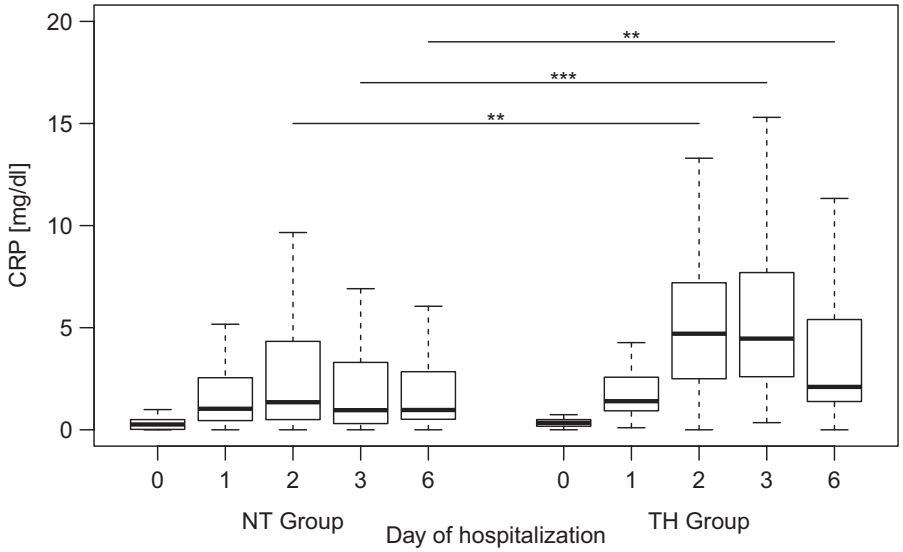

FIGURE 2 Progression of CRP. Data are presented as median [interquartile range, IQR] unless otherwise indicated. 0, day of admission; 1-6, day one to six; $^{**}P < .01$; $^{***}P < .001$

TABLE 2 Coagulation parameters

	In range	total	TH group	NT group	*P* value
PT (40%-115%)	Yes	43 (37.1)	11 (26.6)	32 (73.4)	.096
	No	73 (62.9)	16 (43.3)	21 (56.7)	
PTT (30-42 s)	Yes	14 (18.2)	4 (28.6)	10. (71.4)	.650
	No	63. (81.8)	22 (34.9)	41 (65.1)	
Fibrinogen (170-290 mg/dL)	Yes	18 (23.4)	3 (16.7)	15 (83.3)	.062
	No	59 (76.6)	24 (40.7)	35 (59.3)	
Antithrombin III (80%-120%)	Yes	5 (11.4)	1 (20.0)	4 (80.0)	.154
	No	39 (88.6)	21 (53.8)	18 (46.2)	

Note: Data are presented as numbers (percentages) unless otherwise indicated. *P*-values were calculated using the chi-square or the two-tailed unpaired *t*-test.

Abbreviations: PT, Prothrombin Time; PTT, Partial Thromboplastin Time.

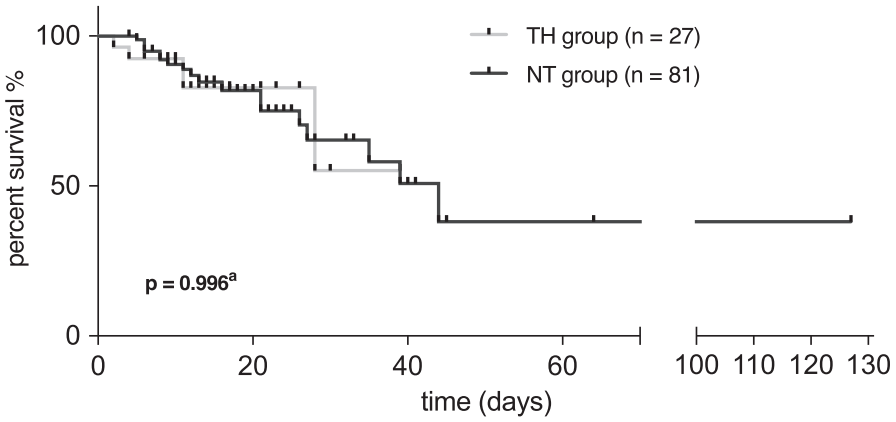

FIGURE 3 Kaplan-Meier estimator of survival. Data are presented as percentages unless otherwise indicated

without finding an overall increased risk for infection,[16] as also described by Scholefield et al[7] Although we found that the incidence of CRP elevation was higher in the TH group, this did neither influence the length of stay itself nor did it seem to be influenced by the length of PICU stay, similar to results reported by Hutchison et al[17] In our analysis, higher CRP levels under hypothermic conditions were found following from day two after admission; this could be interpreted as a consequence of an immunological impairment, an area heavily discussed over the past two decades.[2,3,18] Jenkins et al showed that altered cytokine expression such as interleukin 6 (IL 6), seen in cooled newborn infants, is essential for the release of CRP, consequently, the response might be delayed.[19] However, we would like to emphasise that our study population comprised newborn infants as well as older children and therefore do not exclude the possibility of an underlying infection. According to our retrospective cohort, we were unable to draw the conclusion that age affords an advantage for resistance to infection, as the median age of the TH group was higher than in the NT group. Also there was no difference in the CRP elevation between neonates and older children, independent if they underwent TH or not. Similar results have been found regarding the incidence of infection and length of TH.[5] Polderman (2009) and Geurts (2014) discussed a higher incidence of pneumonia when TH was performed for more than 24 hours.[5,16] Other findings have revealed contradictory statements on rates of infectious complications in adult patients, in contrast to normothermic controls.[8,20] Similarly, other data concerning diagnosed infections during TH on paediatric patients seem inconclusive.[9,16] Grinkevicuite et al reported a high frequency of airway infections in TH-treated children suffering from traumatic or post-hypoxic brain injury.[21] In contrast to our results, Shankaran et al found a nearly equal incidence of infection.[12] A study by Gluckman et al involving 218 infants with neonatal encephalopathy treated with selective head cooling found no significant difference in the frequency of clinically important complications, including infections.[13] In our analysis, there was no significant difference found for possible coagulopathy between the TH and NT group, comparable to an analysis conducted by Tokutomi et al[20] As for overall survival, we found no difference for either of both groups. Other findings demonstrated that mortality rates or severe disabilities in paediatric patients were lower in hypothermic patients in comparison with normothermic patients.[12] In neonates suffering from hypoxic encephalopathy, TH is beneficial in terms of reducing mortality rates and severe motor scores.[13,22] Studies of adult patients after outpatient cardiac arrest also showed decreased mortality after TH.[23,24] Favourable outcomes have been shown to correlate with early-onset nutritional support.[25] Incidence and manifestation of infections, as well as outcomes, have also been influenced by various nutritional methods.[26] Since critically ill neonates and children at our PICU only received enteral feeding with hydrolysed formula, we did not further analyse this parameter. Our data revealed that children during TH have increased CRP levels compared with normothermic controls, as well as more culture-proven infections. These data underline the necessity of continuous monitoring for possible infectious complications when TH is used in a paediatric intensive care setting. Although our analysis is based on the limitations of a retrospective study, we were nevertheless able to report on a sufficiently high number of patients given the long time-range examined (2000-2012), and thus drew our conclusions from a single-centre experience. The amount of published data about the necessity of continuous monitoring of infectious complications while undergoing TH in paediatric intensive care patients is limited, and studies often only focus on newborn infants. With our analyses, we investigated a possible increase of infectious complications during TH and highlight the importance of continuous monitoring during this treatment.

5 | CONCLUSION

Our analyses on the incidence of possible infections during TH, its management and outcome, enhance understanding of its use in paediatric intensive clinical care. The available data underline the critical role of early and continuous monitoring of immunomodulatory mechanisms during induced TH in this manifold patient population. Doing so will improve future management of therapeutic hypothermia in paediatric intensive care patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data sets used and/ or analysed during the current study are available from the corresponding authors upon request.

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