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G. Simbruner
C. Haberl
V. Harrison
L. Linley
A. E. Willeitner

Induced brain hypothermia in asphyxiated human newborn infants: a retrospective chart analysis of physiological and adverse effects

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G. Simbruner (✉) · C. Haberl · A. E. Willeitner
Division of Neonatology, University Children's Clinic, Ludwig-Maximilians University, Lindwurmstrasse 4, D-80337 Munich, Germany
e-mail: simbruner@kk-i.med.uni-muenchen.de
Fax: + 49(89)51 60 44 19

V. Harrison · L. Linley
Mowbray Maternity Hospital, University of Cape Town, Cape Town, South Africa

Abstract *Objective*: To assess the physiological effects and adverse side-effects of induced hypothermia in asphyxiated newborn infants as a base for future controlled, randomized trials.
Design: Retrospective chart analysis with historical controls.
Setting: Tertiary neonatal intensive care unit of the University of Cape Town, South Africa.
Patients: Twenty-one asphyxiated newborns treated with induced hypothermia between September 1997 and February 1998 were compared to 15 asphyxiated newborn infants admitted during March to August 1997. The two groups of infants did not differ in patient characteristics or severity of asphyxia (comparison group vs hypothermia group: Apgar at 5 min 5.3 ± 3.1 vs 5.2 ± 2.3; base deficit 15.6 ± 6.3 vs 11.5 ± 7.2 and Thompson neurological score 10.1 ± 4.0 vs 9.1 ± 3.6).
Interventions: Hypothermia was induced by placing a cap formed from coolpacks, at a temperature of about 10 °C, around the head of asphyxiated newborn infants to maintain the nasopharyngeal temperature between 34 and 35 °C. Hypothermia was maintained for 3 days.
Measurements and results: In the comparison group 4/15 infants died and in the hypothermia group 4/21 died. Hypothermia was induced at a median of 6.0 h (range 45 min to 53 h) post-partum, maintained for an average of 80 h (median 77.5 h, range 22 to 185 h) and resulted in an average nasopharyngeal temperature of 34.6 ± 0.5 °C. Hypothermia reduced abdominal skin temperature from 36.3 ± 0.5 °C to 35.1 ± 0.35 °C ($p = 0.0001$), heart rate from 139 ± 21 to 121 ± 13 beats/min ($p < 0.0001$) and respiratory rate from 67 ± 11 to 56 ± 9 breaths/min ($p = 0.005$). Neither episodes of bradycardia nor dysrhythmias, apnea, clinical signs of bleeding diathesis in the hypothermia group nor differences in the frequency of hypoglycaemia and urinary output, blood in urine or tracheal secretion between the two groups were observed. In the survivors the neurological score, assessed at day 2 and day 5, fell from 10.9 ± 3.5 to 8.1 ± 4.5 in the hypothermia group and rose from 8.1 ± 2.5 to 9.0 ± 3.1 in the comparison group ($p = 0.003$).
Conclusions: Adverse effects of mild hypothermia induced for 3 days in asphyxiated newborns were significantly less than expected from previous reports on neonates with accidental hypothermia.

Key words Induced hypothermia · Newborn infant · Brain asphyxia · Side-effects

Introduction

The incidence of asphyxiated full-term infants still ranges between 2 and 4 infants per 1000 deliveries in high income countries [1, 2] and may be significantly higher in low income countries. In up to 80 % of infants, moderate to severe birth asphyxia results in long-term neurological sequelae and incurs high costs for post-hospital care and severe suffering for families [3, 4].

From animal experiments, a vast body of knowledge demonstrates that lowering brain temperature by 2–3 °C may protect the aspyhxiated brain from neuronal damage and cell death and improve long term neurological outcome [5–7]. In several randomized, controlled clinical trials on adult trauma patients, induced mild to moderate hypothermia for up to 24 h resulted in some beneficial effects [8, 9] without any significant, irreversible side-effects. In a study by Metz et al. [10] on ten traumatized adults, subjected to moderate hypothermia for 24 h, adverse effects such as a temporary decrease in the cardiac index, thrombocytes and creatinine clearance and an elevated serum lipase activity were reported.

Whole body cooling was applied to asphyxiated mature human newborns after delivery by Westin et al. [11] in the 1960s. Several trials treating asphyxiated term infants with hypothermia followed without any details on immediate effects or complications being reported [12]. Recently, head cooling in 12 asphyxiated newborns to two temperature levels was reported not to result in any adverse effects which could be specifically attributed to hypothermia [13].

Accidental hypothermia and hypothermia caused by disease or therapy are known to affect all organ systems [14, 15]. Some of these effects are reversed at normothermia without causing disease or impairment. Other effects like arrhythmias, coagulation disorders or infections may have long-term sequelae [16–21]. Accidentally cooled prematures with a rectal temperature < 34 °C at admission suffered from coagulation disorders, a high incidence of haemorrhage and mortality, while another group of new born prematures with an average rectal temperature of 31 ± 2.7 °C at admission exhibited only transient thrombocytopenia and renal failure [18, 19].

Because of the paucity of data on the effects of induced hypothermia in full term asphyxiated newborns, we retrospectively analysed the charts of 21 aspyhxiated newborns head-cooled for an average of 3 1/2 days to a mean nasopharyngeal temperature between 34 and 35 °C to describe the physiological effects and adverse side-effects in these infants as a base for future controlled, randomized trials.

Patients and methods

Asphyxiated newborn infants admitted to the Neonatal Intensive Care Unit at the Mowbray Maternity Hospital during the period from September 1997 to February 1998 (cooling period) were treated by inducing a brain hypothermia of 34–35 °C. In a retrospective chart analysis these cooled infants were compared to asphyxiated newborn infants admitted during the preceeding period from March to August 1997 (precooling period). The latter group apart from induced hypothermia, was treated the same and served as a comparison group. Asphyxiated newborns were defined as newborns with clinical, biochemical and neurological signs of hypoxic-ischemic encephalopathy (HIE) due to birth asphyxia [1]. The diagnosis of HIE was based on an obstetric history of fetal distress, low Apgar scores, resuscitation, an abnormal base deficit in arterial blood gases on admission and neurological signs post-partum characterized by a severity score [22].

Brain hypothermia was applied as a rescue treatment as an adjunct to standard supportive care and routine intravenous administration of $MgSO_4$, considered to be neuroprotective. Verbal informed consent for inducing hypothermia had been obtained from each mother.

Selection of patients

In the precooling period, 720 newborns were admitted, 35 suffered from HIE. In the cooling period, 678 newborns were admitted, of whom 42 suffered from HIE. In a retrospective chart review by one investigator (H.C.) all data on patients admitted and suffering from birth asphyxia during both periods were screened for a complete data set required for the intended analysis. Fifteen of 35 asphyxiated newborns from the "precooling period" and 21 of 42 asphyxiated newborns from the "cooling period" had been cooled, had the required data set and were analysed. The selection bias was only the availability of complete data sets. Thus, 15 uncooled newborns served as historical controls for the comparison (comparison group) with 21 newborns treated with rescue hypothermia.

Characteristics of patients

The newborns in the hypothermia and comparison groups did not differ in gestational age, birthweight, Apgar scores at 1 and 5 min or in arterial pH, arterial carbon dioxide tension and base deficit at the first blood gases obtained initially at admission. The two groups on the first day of life and before starting cooling did not differ in abdominal skin temperature, heart rate or respiratory rate. The neurological assessment score for HIE [22] was similar in the first and/or second postnatal day in both groups [Table 1]. The degree of HIE in the infants analysed was moderate on the average and did not differ between the groups (comparison group vs hypothermia group: Apgar 5 min 5.3 ± 3.1 vs 5.2 ± 2.3; base deficit 15.6 ± 6.3 vs 11.5 ± 7.2; Thompson neurological scores 10.1 ± 4.0 vs 9.1 ± 3.6). However, within the groups the severity of HIE was inhomogeneous and ranged from mild to severe.

Patient care and monitoring

The newborns of both groups were routinely treated with i.v $MgSO_4$ 0.2 mmol/kg/day for 2 days. Newborns with seizures were initially treated with phenobarbitone 20 mg/kg to a maximum of two doses and then infused with midazolam until seizures had

Table 1 Characteristics of infants in the two groups

	Comparison	Hypothermia	P value
No. of infants	15	21	
Gestational age (weeks)	38.9 ± 2.2	39.4 ± 1.8	NS
Birthweight (gm)	2881 ± 530	3087 ± 488	NS
Apgar at 1 min	3.5 ± 2.8	2.7 ± 2.2 (skewed)	
Apgar at 5 min	5.3 ± 3.1	5.2 ± 2.3	NS
Arterial pH[a]	7.20 ± 0.13	7.24 ± 0.18	NS
Base deficit (mEq)[a]	15.6 ± 6.3	11.5 ± 7.2	NS
Pa CO_2 (mmHg)[a]	26.7 ± 6.6	31.6 ± 10.7	NS
Tskin abd (°C)[b]	36.2 ± 0.5	36.3 ± 0.4	NS
Heart rate (beats/min)	144 ± 14	139 ± 21	NS
Resp. rate (breaths/min)	59 ± 19	67 ± 14	NS
Neurological score (within first 2 days of life)	10.0 ± 4.0	9.1 ± 3.6	NS
Ventilated	6/15 (40%)	13/21 (62%)	NS
Died	4/15 (27%)	4/21 (19%)	NS

[a] Arterial bloodgases in 16/21 (76%) cooled infants and in 9/15 (60%) comparison infants
[b] Abdominal skin temperature in 16/21 (76%) cooled infants and in 13/15 (86%) comparison infants

been absent for 24 h. The midazolam loading dose was 0.1 mg and the maintainance dose 2 µg/kg/min. Midazolam treatment in all patients was terminated on the third postnatal day. No analgesic medication was routinely administered.

The neurological score [22] in both groups was determined at least once during the first 2 days of life and then daily until day 5 in nearly all patients and in some patients up to day 7 or until the death of the infant. Temperatures, heart rate and respiratory rate of spontaneously breathing patients and blood pressure were recorded hourly. Monitoring also included routine recording of blood in tracheal secretions, blood haematocrit and glucose values assessed by test strips (Dextrostix, Ames R and Hemoglucotest, Boehringer R, both methods checked by laboratory tests), recording of the frequency of urinary voiding and testing for blood in urine. The frequency of respirator support, of testing glucose levels and of urinary probe sampling were not significantly different in the two groups.

Induction of hypothermia and management of thermal environment

Hypothermia was induced by placing a cap formed from coolpacks (about 18.5 cm × 15 cm × 2 cm in size) around the head of asphyxiated newborn infants. One cool pack was placed underneath the head, a second placed on the right and the third on the left temple to form a cap around the head. These coolpacks had been kept in a refrigerator at a set temperature of about 10 °C. The coolpacks were exchanged for new, cooled ones, when the nasopharyngeal temperature started to rise above 34.5 to 35 °C.

All infants were nursed in an open infrared radiator heated crib (Air-Shields System 7810; model 2 and Servoscrib 91) in a room with two big glass windows, air-conditioned to a room temperature of 24 to 25 °C. Most of the infants were servocontrolled (abdominal skin temperature = temperature of radiant heater) and the rest were controlled manually to a target skin temperature of 34–35 °C. Among the servocontrolled infants, 60% (9/15) were in the comparison and 62% (13/21) in the hypothermia group. Abdominal skin temperature was recorded in all infants. In addition, in the manually controlled infants the temperature setting at the radiant heater was recorded.

Nasopharyngeal temperature was measured only in cooled infants. This was targeted at a temperature range between 34 and 35 °C and was achieved mainly by the cooling cap, but to some extent also by lowering the radiant heater output. Consequently, both local, selective head cooling and systemic cooling by lowering the temperature of the thermal environment were employed to maintain the target nasopharyngeal temperature during induced hypothermia.

Temperature measurements

Nasopharyngeal temperature was measured by inserting a soft, flexible, thin thermistor probe (Yellow Springs Instruments type 4499E) into the nasopharynx at a depth corresponding to the distance from the alae nasae to the meatus of the ear. The skin temperature was measured with a skin temperature probe fixed with a thin plaster (Micropore) to the lateral side of the abdomen. Care was taken that the probe remained exposed to the environment and that the baby was not lying on it. Nasopharyngeal temperature was documented half-hourly during and until 12 h after the cooling period.

Statistical analysis

Normally distributed data are presented as mean ± 1 standard deviation, skewed data as median and range. For comparison between groups, the Mann-Whitney test, unpaired Student's *t*-test and the Pearson chi-square test was used. The average values of the comparison group during days 1–3 were used for comparison to the hypothermia group cooled for 3 1/2 days post-partum. A p value of < 0.05 was considered significant.

Results

In the hypothermia group, 4 of 21 infants died: 2 of the 4 infants died while being ventilated, one at 44, the other at 63 h post-partum. In the other 2 patients ventilator therapy was stopped at 81 and 108 h, respectively, because of clinical signs of brain death (fixed and dilated pupils, no response to noxious stimuli and no electrical activity on the cerebral function monitor). In the comparison group, 4 of 15 died between 4 and 40 h post-par-

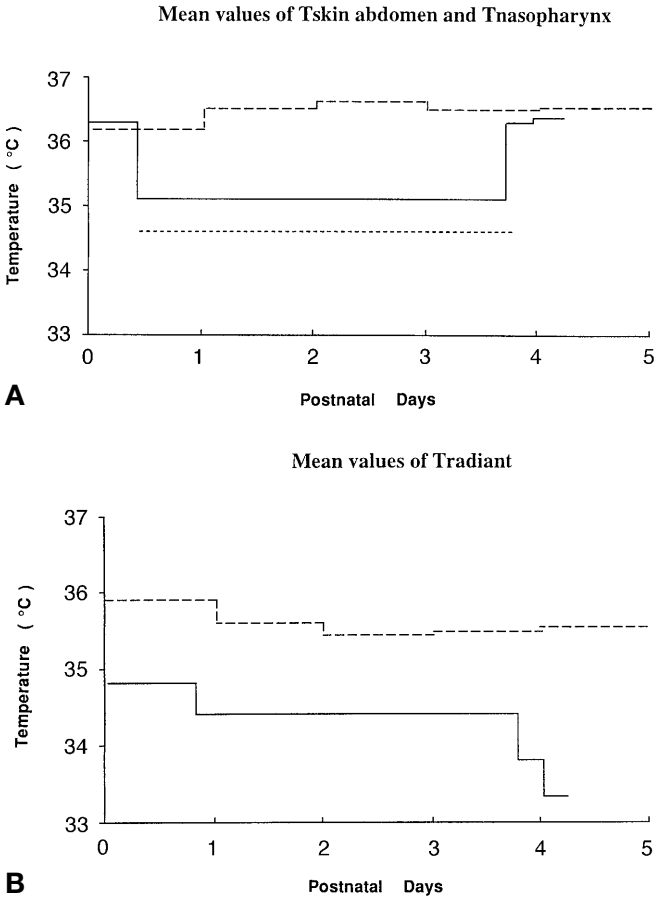

Fig. 1 **A** Mean values of abdominal skin temperature in the comparison group *dashed line* and in the hypothermia group full line. Mean value of nasopharyngeal temperature of hypothermia group *dotted line*. **B** Mean values of temperature of radiant warmer in the comparison group *dashed line* and the hypothermia group (full line)

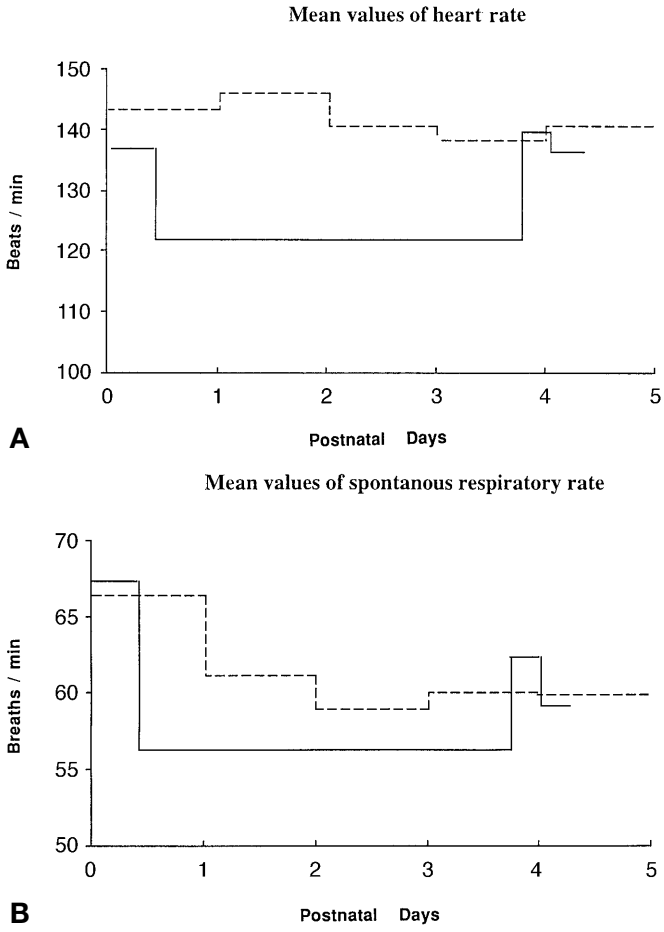

Fig. 2 Mean values of heart rate **(A)** and spontaneous respiratory rate **(B)** in the comparison group (*dashed line*) and the hypothermia group (full line)

tum. Mortality and frequency of ventilator support was not statistically different (Table 1).

Hypothermia was started at a median of 6.0 h (an average of 9.0 h, range 45 min to 53 h) post-partum and was terminated at an average of 89 h (median 77 h, range 28 to 197 h) post-partum. The average time of induced hypothermia was 80 h , ranging from 22 to 185 h.

The time course of nasopharyngeal (Tnaso), abdominal skin (Tskin abd) and radiant heater temperature (Trad) are shown in Fig. 1. Tabd was similar in both groups on day 1 and before inducing hypothermia. Induction of hypothermia by the cooling cap and radiant heater regulation resulted in a mean Tnaso of 34.6 ± 0.5 (inter-individual range 33–36 °C; lowest single intra-individual value 29 °C). In 2 infants, in whom both Tnaso and rectal temperature (Trect) had been measured during cooling, the mean difference (Tnaso – Trect) between these two temperatures was –0.6 ± 0.3 °C

Induced hypothermia reduced Tskin abd from 36.3 ± 0.5 °C to 35.1 ± 0.35 °C ($p = 0.0001$). During hypothermia, lowest Tskin abd recorded in an individual infant was 30 °C. Six hours after ending the cooling the Tskin abd had returned to pretreatment levels and was not different from the comparison group. In the comparison group Tskin abd did not change over the first 5 postnatal days. The Trad was about 1 °C lower in the hypothermia group than in the comparison group and was lowered even further after cooling.

No life-threatening events or adverse effects which could be directly attributed to induced hypothermia were reported. Heart rate was identical in both groups on day 1 and before the start of cooling (hypothermia 139 ± 21 beats/min vs comparison 143 ± 14 beats/min; NS). Heart rate dropped to an average of 121 ± 13 beats/min ($p = 0.0001$) or 13% from baseline during the period of cooling, while it remained constant in the comparison group. Within 6 h of ending cooling it returned to levels not different from control (Fig. 2). Simi-

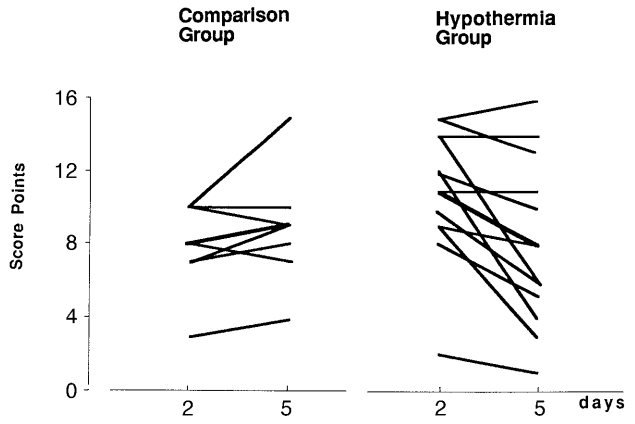

Fig. 3 Changes of Thompson score values between postnatal days 2 and 5 in the comparison group and in the hypothermia group

larly, respiratory rate was 67 ± 11/min in the hypothermia group and 66 ± 10 /min in the comparison group (NS) before cooling and on day 1. Respiratory rate fell to 56 ± 9 breaths/min ($p = 0.005$) or 16% from baseline during induced hypothermia. Within 6 h of cooling, the respiratory rate returned to precooling levels and to the levels similar to those of the comparison group (Fig. 2). The respiratory rate of the comparison group did not significantly change over the first 5 postnatal days.

The incidence of hypoglycaemia (< 2.2 mmol/l) in the hypothermia group was not statistically significantly different when compared to the comparison group [hypothermia group 6.7% (25/ 372 tests) vs comparison group 4.5% (10/224 tests) $p = 0.076$]. There was no difference in the frequency of blood observed in urine samples or in tracheal aspirates. Of 857 urine samples tested, 82 (9.6%) were positive for blood in the hypothermia group and in the comparison group 57 of 506 (11.2%) ($p = 0.91$). Tracheal suction yielding a bloody tracheal aspirate was only reported in the comparison group.

Among the survivors, 13 of 17 infants in the hypothermia group and 8 of 11 infants in the comparison group had a data pair of neurological assessments on day 2 and day 5 (Fig. 3). During that time interval, the neurological assessment score fell from 10.9 ± 3.5 to 8.1 ± 4.5 in the hypothermia group and rose from 8.1 ± 2.5 to 9.0 ± 3.1 in the comparison group ($p = 0.003$). In the hypothermia group, the score decreased in 10 infants, remained constant in 2 and increased in 1, while in the comparison group it decreased in 2, remained constant in 2 and increased in 4.

Discussion

In this retrospective chart analysis, we found that an induced hypothermia of 34.6 °C for an average duration of 3 1/2 days resulted in no adverse effects in asphyxiated infants. This study was not aimed at detecting differences in neurological outcome but at describing immediate physiological effects and adverse effects of brain and body hypothermia induced in asphyxiated infants as a base for designing protocols for controlled randomised trials. For example, it would be difficult to justify subjecting newborns with mild to moderate asphyxia, whose spontaneous recovery rate is reported to range from 50 to 80%, to hypothermia if induced hypothermia were associated with many irreversible and severe side-effects.

Mild hypothermia has been defined as a temperature between 36.5 and 34 °C [15]. In our hypothermia group, the Tnaso was reduced to 34.6 ± 0.5 °C – thus reduced to mild hypothermic levels. The temperature in our hypothermic group was also lower than that reported by Gunn et al. [13] of 36.3 °C for a minimal and 35.7 °C for a mild cooling group. In healthy mature newborns nursed in cots, we found a mean Tnaso, measured at nose-ear distance, of 36.6 ± 0.5 °C (Ko H. H., Simbruner G., unpublished results). We therefore assume that the head temperature was reduced by approximately 2 °C in hypothermic infants compared to normals.

In hypothermia, heart and breathing rates [23] and cardiac function [10, 24] are known to be decreased, peripheral vascular resistance [25] to be increased and cardiac distribution to be altered [24] depending on the level and duration of hypothermia. In our newborns, mild hypothermia reduced heart and respiratory rates by 13 and 16%, respectively. This is in contrast to reports in infants with accidental cooling, where heart and metabolic rates increased at temperatures between 35 and 31 °C and only decreased below 31 °C [14]. During the 3–1/2-day hypothermia, sinus rhythm was maintained in the infants. No episodes of bradycardia and dysrhythmias were observed. It is thus very unlikely that ectopic beats, atrial or ventricular flutter, or fibrillation were missed. Similarly, in an electrocardiographic study, sinus rhythm was present in 17/18 adults suffering from accidental mild hypothermia (> 32 °C) [16]. Atrial fibrillations were observed only at body temperatures between 32 and 26 °C, and these reverted to sinus rhythm before or at normothermia. The respiratory rate of spontanous breathing decreased during hypothermia as expected [23], but no infant developed apnea. Consequently, prophylactic intubation and ventilation do not seem justified on the grounds of our observations. The decrease in both heart and respiratory rates was due to a regulatory effect of induced hypothermia, not of asphyxia, as heart and respiratory rates immediately returned to control values after the end of hypothermia.

Both, hypo- and hyperglycaemia may occur in hypothermic patients [26]. Adverse effects of hypothermia on the pancreas have been reported [10]. In our study population, a trend of an increased incidence of hypoglycaemia in the hypothermia group was obvious (6.7 vs 4.5 %; $p = 0.076$), but the difference failed to achieve statistical significance at the 5 % level. This lack of difference might be due to the frequency of glucose disturbances being similar in the treated and untreated group or to treatment to avoid hypoglycaemia. Increases in catecholamines and glucagon during hypothermic stress increase glycolysis and could be responsible for compensating for falling glucose levels or for increasing glucose levels [10]. Close monitoring of hypoglycaemia is certainly of great importance during hypothermia, as its adverse consequence of causing neurological damage could offset the gain by hypothermia [27].

Hypothermia is known to increase urinary output due to decreased reabsorption and reduction in antidiuretic hormone [10, 28]. No difference in the rate of urine voiding was observed between the hypothermia and comparison group. Hypothermia is also known to cause coagulopathies. Infants with a rectal temperature < 34 °C on admission had a higher mortality than controls (7/19 vs 1/19), and in 3 of 7 deceased infants necropsy of hypothermic infants revealed massive cerebral haemorrhage [18]. Pulmonary haemorrhage and haematuria have been reported in newborns. In a series of 14 infants suffering from the effects of hypothermia, pulmonary haemorrhage was found to be the major cause of death in 5 babies [17]. No single infant in our analysis had developed overt clinical signs of coagualtion disorders, pulmonary haemorrhage or other signs such as blood in urine samples and blood in tracheal secretions, despite 34.5 °C hypothermia for an average of 3 1/2 days.

Hypothermia may significantly alter bleeding time, thrombin clotting time and prothrombin time and slightly lower thrombocytes, all returning to normal at normothermia [19]. In our chart analysis, we were able to report on the clinically observable signs of bleeding diatheses, but not on the specific coagulation status during or after induced hypothermia. However, the study of Staab et al. [20] emphasises that assessing bleeding diathesis clinically is more relevant than laboratory coagulation tests at 37 °C. Meaningful coagulation tests would have to be done at water bath temperatures corresponding to the actual one of the hypothermic patient.

Whether the cooling of the head to a Tnaso of 34.5 °C had an immediate beneficial effect on the neurological course of asphyxia remains unknown. The statistically significant different rate of changes in scores between days 2 and 5 indicate that the results are at least not counterintuitive to the expectations of improved outcome raised from animal experiments and the few clinical trials. However, these improvements observed in our patients and characterised by a subjectively applied score might express this very bias of the investigators. The results showing a treatment benefit may differ between 24 % in unblinded and 9 % in blinded, randomised trials [29].

In conclusion, adverse effects during and after induced long-term hypothermia in the surviving asphyxiated newborns were significantly less than expected from previous reports on neonates with accidental hypothermia [14, 17–19]. The absence of clinical complications detectable by routine clinical surveillance in infants kept at mild hypothermic levels for a mean of 3 1/2 days might justify including infants with mild to moderate aspyhxia, where treatment effect is thought to be higher [9], in scientific hypothermia trials.

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