

ORIGINAL ARTICLE

Strategies for reducing the incidence of skin complications in newborns treated with whole-body hypothermia

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Objective: To present the results of a strategy designed to reduce the incidence of skin complications in newborns with hypoxic–ischemic encephalopathy treated with moderate whole-body hypothermia. **Design:** Retrospective study. **Setting:** Neonatal Intensive Care Unit (NICU). **Patients:** Thirty-nine neonates cooled in the considered period. **Intervention:** Starting from January 2008, for neonates treated with moderate whole-body hypothermia (33.5 °C), the cooling system was set in “automatic servo-controlled mode (ACM)”, where the temperature of the circulating water could vary between 4 °C and 42 °C. Starting from January 2009, cooling blankets were used in another type of automatic mode, the “gradient variable mode (GVM)”, where the circulating water was maintained at a specific pre-set gradient towards the patient’s body temperature, and a specific nursing protocol (NP) was adopted. **Measurements and main results:** Two of the eleven newborns treated with the “ACM” exhibited skin complications compatible with subcutaneous fat necrosis (SFN). None of the twenty-eight newborns treated with the “GVM” exhibited skin complications. A comparison of the biochemical and hematological data between these two groups revealed that newborns treated after the adopting of a NP and the “GVM” showed lower serum protein C and calcium levels, and higher platelet levels. **Conclusions:** Our data suggest that newborns undergoing therapeutic cooling may benefit from a specific NP and correct cooling unit setting. Should further studies confirm our data, this nursing approach could be easily adopted.

Keywords: asphyxia, hypothermia, hypoxic-ischemic encephalopathy, newborn, subcutaneous fat necrosis

Introduction

Perinatal hypoxic–ischemic encephalopathy is still the single most important cause of serious brain injury in newborns. Recent trials have demonstrated that moderate hypothermia (MH) (rectal or esophageal temperature 33–34 °C) in asphyxiated neonates, if started within 6 h after birth and protracted for 72 h, can significantly improve survival and reduce brain injury at 18 months [1]. Therefore, therapeutic hypothermia has recently been included in

the Guidelines of International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science [2].

Cooling needs to be initiated as soon as possible after asphyxia [3]. MH can be started passively (by stopping the heating) or by applying ice bags to the head and body before and during transfer of the neonate to the referring hospital, where active MH can be obtained with selective head or whole-body cooling [3].

MH is generally well-tolerated. Side effects, represented by sinus bradycardia and thrombocytopenia, are transient and reversible with rewarming [4]. Early studies suggested an increase in hypotension requiring inotrope infusion in newborns treated with hypothermia [4], but a subsequent analysis demonstrated that MH does not affect arterial blood pressure [5]. Moreover, several cases of subcutaneous fat necrosis (SFN) and cold panniculitis in newborns undergoing MH have recently been described [6–12]. A recent survey reported a prevalence of ~1% among infants subjected to MH [13].

In this study, we report the onset of skin complications in two asphyxiated newborns treated with whole-body hypothermia, and illustrate the results of our strategy to reduce their incidence using a nursing protocol (NP) and a specific surface-cooling system adjustment. We analyzed the hypothesis that frequent mobilization of infants and the limiting of abrupt temperature changes of the water circulating in the mattresses might reduce the incidence of SFN and the inflammation markers.

Materials and methods

Patients

Starting from January 2008, asphyxiated newborns with gestational age ≥ 36 weeks and birth weight $\geq 1,800$ g admitted to the 16-bed Neonatal Intensive Care Unit (NICU) of the A. Meyer University Children’s Hospital were treated with moderate whole-body hypothermia when the following criteria were ascertained: (i) metabolic criteria: Apgar score ≤ 5 at 10 min, or persisting need for resuscitation, including endotracheal intubation or mask ventilation for more than 10 min after birth, or acidosis (pH ≤ 7.0 and/or base deficit ≥ -16 mmol/l in umbilical cord blood or arterial, venous, or capillary blood) within 60 min after birth; (ii) neurological criteria: moderate to severe encephalopathy

consisting of altered state of consciousness (irritability, lethargy, stupor, or coma) and ≥ 1 of the following signs: hypotonia, or abnormal reflexes including oculomotor or pupillary abnormalities, absent or weak sucking, or clinical seizures. Cooling was started within 6 h after birth and maintained for 72 h at 33.5 °C. Newborns older than 6 h of age at the time of evaluation and newborns with major congenital abnormalities or evidence of encephalopathy other than hypoxic-ischemic encephalopathy were excluded. Neonates treated with deep hypothermia were also excluded from this study. Outborn patients were initially cooled to around 35 °C of core body temperature at their birth hospital, by stopping the heating or applying ice bags near head and body during transfer to the NICU.

Upon arrival, newborns were cooled to 33.5 °C using a cooling blanket (Blanketrol® III, Hyper-hypothermia System; Cincinnati Sub-Zero, Cincinnati, OH), connected by a servomechanism to an esophageal probe. Newborns were lying on this cooling blanket that was covered by a thin sheet. Rectal temperature was continuously monitored by a probe connected to a cardiomonitor (Infinity Delta; Dräger Medical System, Telford, PA) for simultaneous measurement of respiratory rate, heart rate, blood pressure, and oxygen saturation. Skin temperature was monitored with a skin probe on the abdominal wall by the radiant warmer thermal sensor or a temperature-monitoring unit (Mon-a-therm[®]; Mallinckrodt Medical, St Louis, MO). After 72 h of hypothermia, newborns were gradually rewarmed to 36.5–37 °C during the following 6–12 h by increasing the automatic control set-point of 0.5 °C per hour. Newborns who complied with the entry criteria were enrolled until August 2009 in a pilot study for evaluating the safety of oral topiramate administration associated with hypothermia [14], and those admitted after February 2010 were enrolled in a randomized controlled study for evaluating the neuroprotective efficacy of combination treatment with topiramate and hypothermia [15].

Surface-cooling system

The cooling blanket unit used in our NICU can be set in manual control mode so that the operator can establish *a priori* the temperature of the circulating water, or in automatic mode, where the target temperature is reached with a servomechanism by heating or cooling the circulating water in relation to the newborn's rectal or esophageal temperature.

From January to December 2008, patients were cooled using the cooling blanket in automatic mode, called "auto control mode" (ACM). With this type of mode the operator sets the patient's target temperature (33.5 °C according to our protocol); if the patient's actual temperature is lower than the target, the unit can heat the circulating water up to a maximum temperature of 42 °C (107.6 °F). Similarly, if the patient's actual temperature is higher than the target, the unit can cool the circulating water down by a minimum of 4 °C (39.2 °F). With this operating mode, the newborn's skin can be exposed to rapid and abrupt temperature changes. During this year two cases of SFN were observed.

Starting from January 2009 to December 2011, along with the application of the specific NP (see below) the cooling blanket was also used in another type of automatic mode, the so-called "gradient variable mode" (GVM) plus smart function. In this mode, after reaching the desired set-point temperature of 33.5 °C, the cooling blanket can be used to gradually control the patient's temperature by maintaining the circulating water temperature at a specific pre-set gradient towards the patient's body temperature. The objective was to expose the skin of newborns to slight temperature changes. In our unit a gradient of 5 °C was chosen: meaning that the water can only be heated to 38.5 °C (+5 °C) or cooled down to 28.5 °C (–5 °C). However, by activating the

"smart" function, the water temperature gradient can be automatically increased by 5 °C every 30 min until achieving the target.

NP

From January to December 2008, newborns treated with MH were managed according to a nonspecific NP, which provided only sporadic turning of newborns to prevent bedsores. Starting from January 2009, all cooled newborns were subjected to a specific NP. This included the mobilization of neonates with alternating pronation and supination every 3 h during cooling in order to avoid prolonged contact of a specific skin area with the cooling surface.

Study design

We retrospectively compared biochemical parameters and the incidence of adverse skin effects between the two groups of hypothermic newborns treated with different cooling blanket modes and different NPs. The following blood tests were foreseen at T_0 (time zero, when cooling was initiated), T_{24} , T_{48} , T_{72} , and 24 h after the rewarming process (T_{96}) as planned in previous prospective studies [14,15]: blood gas analysis (corrected for body temperature), lactate, glucose, serum electrolyte level (sodium, potassium, chloride, calcium), liver (aspartate and alanine aminotransferase, total protein, coagulation tests) and renal function tests (blood urea nitrogen, creatinine), creatine-kinase, creatine-kinase MB isoenzyme, complete cell blood count, and C-reactive protein (CRP) level. These laboratory tests were planned.

Skin injuries were recorded via retrospective analyses of medical and nursing records of patients treated with hypothermia, and with photographic documentation. Skin injuries were considered device-related when they were in contact with a cooling blanket, and not present at the time of hospital admission.

For newborns with SFN, a weekly or biweekly monitoring of total and ionized calcium levels was planned for at least 6 months or until the fat necrosis resolved.

Statistical analysis

The primary endpoint was the incidence of skin injury. The secondary endpoint was the different incidence of biochemical abnormalities between newborns treated with different nursing approaches. Differences in means between the cohorts were analyzed using the two-tailed Student's *t*-test, with significance recognized at the $P < 0.05$ level.

The pilot study and the randomized controlled study regarding hypothermia [14,15] were approved by the local ethics committees. Written informed consent was obtained from both parents of all enrolled newborns. Consent to show the photographs of the two infants with SFN was obtained from their parents.

Results

During this period, thirty-six newborns admitted to our NICU for perinatal asphyxia met the admission criteria and were treated with whole-body hypothermia. All the newborns were cooled during transfer to the NICU, by stopping the heating; no one was cooled applying ice bags. Eleven newborns were treated using the ACM and twenty-eight neonates were cooled with the GVM plus the specific NP. Demographic data of these newborns are shown in Table I. Infant's core temperatures were similar between the two groups during cooling (Figure 1a). Also mean blanket temperature was similar in both groups, but its fluctuation was significantly higher in the ACM group (Figure 1b).

Table I. Demographic data of newborns treated with whole-body hypothermia.

	Newborns treated with the ACM (n = 11)	Newborns treated with GVM plus specific NP (n = 28)	P
Male, n (%)	6 (54.5)	19 (67.9)	0.449
Gestational age (weeks), mean \pm SD ^a	39.4 \pm 1.7	38.2 \pm 2.8	0.235
Birth weight (g), mean \pm SD	3,249 \pm 656	3,102 \pm 468	0.450
Cesarean section, n (%)	7 (63.6%)	16 (57.1%)	0.719
Stained amniotic fluid, n (%)	7 (63.6%)	12 (42.9%)	0.295
Outborn, n (%)	11 (100.0%)	28 (100.0%)	N/A
Apgar score (1 min), mean \pm SD	2.4 \pm 2.1	2.0 \pm 2.0	0.493
Apgar score (5 min), mean \pm SD	3.9 \pm 2.7	4.1 \pm 2.2	0.803
Crib score, mean \pm SD	4.4 \pm 2.1	3.8 \pm 2.0	0.493
Arterial pH, mean \pm SD	6.90 \pm 0.18	6.84 \pm 0.16	0.310
Arterial BE, mean \pm SD	-19.5 \pm 5.9	-22.5 \pm 7.5	0.256
Arterial lactic acid (mmol/l), mean \pm SD	15.0 \pm 4.7	16.3 \pm 4.5	0.526
Hour hypothermia beginning, mean \pm SD	3.6 \pm 1.2	3.6 \pm 1.4	0.978
Subcutaneous fat necrosis, n (%)	2 (18.2)	0 (0.0)	0.014

ACM, auto control mode; BE, base excess; GVM, gradient variable mode; N/A, not applicable NP, nursing protocol.

^aCalculated from maternal menstrual history, obstetrical data or by Ballard's score.

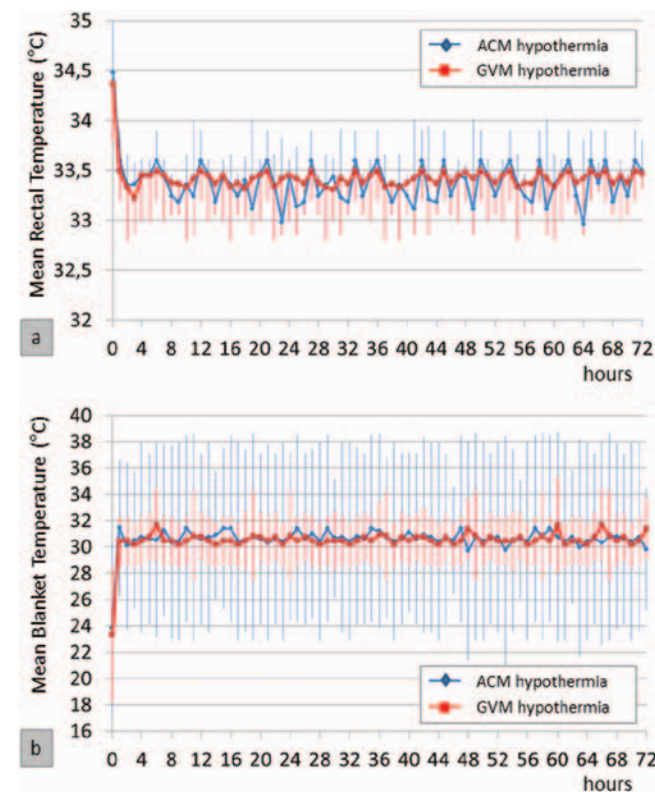


Figure 1. Mean rectal and blanket temperature in both groups. (a) Mean rectal temperatures and (b) mean blanket temperature in newborns treated with ACM or GVM hypothermia during the 72-h intervention period. The vertical bars indicate SD. ACM, auto control mode; GVM, gradient variable mode.

Within the group of newborns treated with the ACM mode, two neonates developed skin complications.

Patient 1

A full-term male infant born by urgent cesarean section for placental abruption started hypothermia at 5 h of age. About 20 days after rewarming a nontender area of erythematous indurated plaques was observed on the lateral surface of the neck and back (Figure 2a). During the following days multiple indurated areas were palpable in the subcutaneous tissues of the trunk and arms. The skin over the indurated areas was bluish-purple. High levels of blood CRP (up to 15.2 mg/dl; normal value <0.5), not accompanied by a concurrent rising of procalcitonin, were observed. Platelet count and calcium level remained within the normal range during hospitalization and over the following weeks. Plasma CRP levels returned to normal range in about 40 days; skin recovery was complete, without scarring.

Patient 2

A full-term female infant born by instrumental vaginal delivery with application of vacuum extractor due to meconium-stained amniotic fluid, started hypothermia at 2 h of age. About 7 days after rewarming, multiple and confluent areas of bluish-purple indurated plaques were initially observed on the back (Figure 2b), and later extended to the posterior surface of thighs and armpits. The buttocks, protected by the diaper, were not affected. Blood CRP increased to 9.2 mg/dl, with normal levels of procalcitonin. Platelet count and calcium level were slightly reduced to $51 \cdot 10^9/L$ after 72 h of hypothermia and 8.3 mg/dl after 48 h, respectively; both parameters normalized in a few days. Plasma CRP levels returned to normal range in about 20 days; skin recovery was complete, without scarring.

No newborns developed skin lesions in the group treated with the GVM plus smart function associated with the adopting of a NP.

The statistical analysis of the measured biochemical variables showed no significant differences between the two groups before beginning hypothermia (Table II). During cooling, some variables became statistically different. After 48 h of hypothermia in the group of newborns treated with ACM, the CRP levels remained significantly higher until after 24 h of rewarming, after 24 h of hypothermia, the platelet count remained significantly lower until after 24 h of rewarming, and after 72 h of hypothermia, the calcium levels remained significantly higher until after 24 h of rewarming (Figure 3). These differences remained even when the data of the two newborns with SFN were excluded from the ACM group.

Discussion

SFN of the newborn is a rare, inflammatory, transient and self-limiting panniculitis typically present within the first few days or weeks of life with erythematous-violaceous, subcutaneous nodules or plaques, localized usually on the back, arms, buttocks, thighs or cheeks [16,17]. Although its pathogenesis is not fully known, it occurs almost exclusively in full-term or post-term neonates with normal size for dates or macrosomia. Most of these have an history of perinatal stress, local ischemia following trauma or pressure injury due to macrosomia and dystocic labor [17]. Maternal risk factors include gestational diabetes, preeclampsia, dyslipidemia, and maternal exposure to cocaine [18] or calcium antagonists [19] during pregnancy. However, other authors have recently suggested novel predisposing genetic risk factors, such as familial dyslipidemia or thrombophilia [16].



Figure 2. Subcutaneous fat necrosis. Erythematous and indurated plaques on the back of (a) patient 1 and (b) patient 2 after direct contact with the cooling blanket.

The high incidence of SFN in infants exposed to hypothermia has recently suggested that “cold stress” could play an important role in its pathogenesis [20]. SFN has been described in newborns following hypothermia when abandoned on the street [21] or exposed to cold weather [22]. Moreover, cases of SFN have been observed in newborns treated with applications of ice bags for supraventricular tachycardia [23–26], or subjected to whole-body cooling before being placed on cardiopulmonary bypass for cardiovascular surgery [27–30]. Neonates have an increased risk of developing SFN due to the different composition of fatty acid concentrations. It has been postulated that the higher percentage of the saturated to unsaturated fats ratio in the brown fat of newborns

compared to the adult yellow fat of older children has an increased tendency to crystallize with hypothermic injury. In fact, the melting point of palmitic acid (the main saturated fatty acid) is around 63 °C, significantly higher than the melting point of the oleic acid (the main unsaturated fatty acid) (13 °C). This difference could explain why a small decrease in the temperature of newborns may result in solidification and crystallization of their fat [27,28,30].

More and more cases of SFN are currently being reported in infants treated with whole-body therapeutic hypothermia following perinatal asphyxia [6–13]. In infants cooled with ice bags and those treated with whole-body hypothermia using cooling blankets, skin lesions have been reported in areas subjected to contact with the surface of the cooling devices, as observed in both of our patients. Skin lesions have been reported in ~20% of adult patients cooled with surface-cooling devices, even though only 6% were device-related [31]. These injuries were also more frequent in patients in shock-requiring vasopressors, or with a poor left ventricular ejection fraction, suggesting that cutaneous blood flow may play an important role [31]. In short, general ischemia after perinatal asphyxia and local ischemia after dystocic labor are both likely to play a key role in the development of SFN; however, skin-surface-cooling, inducing cutaneous and visceral vasoconstriction [32], may also lead to local ischemia and hypoxemia, thus causing the onset of SFN.

We hypothesized that wide and rapid changes of circulating water from cold to hot in cooling blanket, as observed mainly in newborns cooled with ACM hypothermia (Figure 1b), together with persistent pressure on the same skin regions, may compromise local perfusion, leading to local hypoxemia and subsequently putting these infants at risk of skin lesions. For these reasons we investigated the efficacy of our strategy, focusing on periodic mobilization and a gentler cooling blanket setting, in order to avoid abrupt temperature changes. Our experience is therefore very encouraging considering that after adopting this combined protocol the incidence of SFN was nil.

Nevertheless, this study has important limitations. First, the sample sizes are too small to draw statistically significant conclusions. This means that this study can only provide suggestions and recommendations for broader studies. Second, the patients studied had clinical features consistent with SFN, but they did not undergo biopsies or histological examinations necessary for differential diagnosis of cold panniculitis [23]. In fact, although both diseases may be clinically indistinguishable [24], their histopathologic findings are different [20]. This means that we can only draw the general conclusion that our protocol reduces the risk of skin damage. Third, the simultaneous introduction of a NP and a new cooling mode makes it difficult to determine which was the most effective procedure.

Even though SFN is usually a self-limiting disease that resolves within a few weeks or months without scarring, at times rare systemic complications including anemia, thrombocytopenia, hypoglycemia, hypertriglyceridemia, and hypercalcemia may occur [33]. Hypercalcemia, which has been reported to develop in approximately one-third of newborns with SFN [17] but also in over 50% [16] is a very serious complication because it can also be fatal. It usually occurs between 2 and 16 weeks, when SFN begins to resolve and may either be asymptomatic or manifest with failure to thrive, lethargy, irritability, hypotonia, vomiting and, in severe cases, calcification of the soft tissues. Nephrolithiasis, nephrocalcinosis, renal failure, metastatic calcification in the pericardium and brain, and also cardiac arrest have been described [34–36]. Some authors reported an association with elevated prostaglandin levels that can lead to osteoclast activation and calcium release from granulomas or necrotic fat [37]. For others, hypercalcemia

Table II. Blood parameters in infants cooled with auto control mode (ACM) or gradient variable mode (GVM) plus specific nursing protocol (NP).

		Pre	24 h	48 h	72 h	24-h post-rewarming
pH ($-\log[H^+]$)	ACM	7.242 \pm 0.07	7.338 \pm 0.07	7.330 \pm 0.05	7.362 \pm 0.09	7.391 \pm 0.07
	GVM + NP	7.209 \pm 0.11	7.321 \pm 0.06	7.328 \pm 0.06	7.322 \pm 0.09	7.383 \pm 0.05
PCO ₂ (mm Hg)	ACM	38.0 \pm 12.2	45.7 \pm 10.1	48.3 \pm 8.4	44.5 \pm 9.4	42.3 \pm 6.1
	GVM + NP	35.2 \pm 15.2	43.2 \pm 7.4	45.4 \pm 9.9	47.8 \pm 12.5	43.1 \pm 8.0
PO ₂ (mm Hg)	ACM	62.5 \pm 26.7	70.6 \pm 32	69.4 \pm 19.3	91.7 \pm 22.6	82.3 \pm 24.2
	GVM + NP	80.1 \pm 27.3	79.5 \pm 22.1	73.6 \pm 29.9	78.0 \pm 31.2	72.5 \pm 19.2
BE (mmol/l)	ACM	-10.7 \pm 3.2	-1.5 \pm 3.0	-0.5 \pm 3.9	-0.4 \pm 4.3	0.8 \pm 4.4
	GVM + NP	-12.6 \pm 5.4	-4.1 \pm 3.8	-2.8 \pm 3.2	-2.1 \pm 3.9	0.1 \pm 3.6
HCO ₃ (mmol/l)	ACM	16.0 \pm 2.4	22.5 \pm 2.7	23.4 \pm 3.0	24.0 \pm 3.7	25.0 \pm 3.7
	GVM + NP	15.5 \pm 4.1	21.7 \pm 2.3	22.6 \pm 2.8	22.8 \pm 2.7	24.3 \pm 3.2
Lactate (mmol/l)	ACM	9.5 \pm 5.3	4.1 \pm 2.2	2.6 \pm 1.3	2.0 \pm 1.5	1.8 \pm 0.8
	GVM + NP	10.7 \pm 6.5	4.0 \pm 3.3	3.0 \pm 3.3	1.9 \pm 1.4	1.7 \pm 1.0
Glucose (mg/dl)	ACM	108 \pm 41	83 \pm 23	72 \pm 14	68 \pm 16	79 \pm 18
	GVM + NP	118 \pm 59	92 \pm 28	81 \pm 21	82 \pm 21	90 \pm 17
Na (mmol/l)	ACM	135 \pm 3.0	134 \pm 4.3	134 \pm 4.8	136 \pm 3.5	136 \pm 4.7
	GVM + NP	135 \pm 5.0	133 \pm 4.7	132 \pm 5.1	134 \pm 4.6	137 \pm 5.1
K (mmol/l)	ACM	4.3 \pm 0.8	4.2 \pm 0.5	4.1 \pm 0.7	3.8 \pm 0.6	3.7 \pm 0.7
	GVM + NP	4.0 \pm 0.5	4.2 \pm 0.7	4.3 \pm 0.9	4.1 \pm 0.8	3.7 \pm 0.6
Ca (mg/dl)	ACM	9.0 \pm 1.3	8.8 \pm 0.7	8.7 \pm 0.7	9.6 \pm 0.8*	9.5 \pm 0.7*
	GVM + NP	8.7 \pm 0.4	8.7 \pm 0.7	8.7 \pm 0.7	8.7 \pm 0.8*	8.6 \pm 0.9*
Creatinine (mg/dl)	ACM	0.98 \pm 0.2	0.95 \pm 0.3	0.90 \pm 0.5	0.85 \pm 0.5	0.95 \pm 0.7
	GVM + NP	1.27 \pm 0.4	1.17 \pm 0.4	0.86 \pm 0.4	0.76 \pm 0.3	0.80 \pm 0.3
Urea nitrogen (mg/dl)	ACM	24.1 \pm 6.9	27.8 \pm 9.7	27.6 \pm 16.8	31.1 \pm 20.7	30.2 \pm 18.1
	GVM + NP	27.7 \pm 11.2	35.8 \pm 12.9	37.4 \pm 17.2	34.6 \pm 17.9	32.3 \pm 15.5
Aspartate aminotransferase (U/l)	ACM	140 \pm 78	326 \pm 282	133 \pm 73	146 \pm 81	70 \pm 41
	GVM + NP	163 \pm 110	153 \pm 148	101 \pm 42	76 \pm 35	57 \pm 27
Alanine aminotransferase (U/l)	ACM	77 \pm 45	121 \pm 57	61 \pm 36	87 \pm 21	45 \pm 17
	GVM + NP	86 \pm 52	101 \pm 68	71 \pm 49	75 \pm 35	51 \pm 32
Total protein (g/dl)	ACM	5.3 \pm 1.3	4.8 \pm 0.8	4.9 \pm 0.7	5.1 \pm 0.8	5.2 \pm 0.7
	GVM + NP	5.7 \pm 0.5	5.2 \pm 0.7	5.2 \pm 0.6	5.0 \pm 0.5	5.2 \pm 0.6
Creatine-kinase (U/l)	ACM	1,488 \pm 839	2,324 \pm 1,497	1,286 \pm 997	1,588 \pm 590	326 \pm 150
	GVM + NP	1,879 \pm 581	1,667 \pm 978	1,601 \pm 1,016	1,575 \pm 787	481 \pm 321
Creatine-kinase MB (U/l)	ACM	84 \pm 62	69 \pm 42	74 \pm 54	74 \pm 41	63 \pm 38
	GVM + NP	69 \pm 42	108 \pm 49	104 \pm 80	71 \pm 41	63 \pm 34
Hemoglobin (g/dl)	ACM	15.1 \pm 5.5	15.7 \pm 3.4	14.9 \pm 3.0	14.8 \pm 3.2	13.3 \pm 2.6
	GVM + NP	16.3 \pm 2.3	15.6 \pm 2.8	14.8 \pm 2.6	13.7 \pm 2.5	12.1 \pm 2.6
White blood cell count ($10^9/l$)	ACM	20.9 \pm 10.5	11.9 \pm 4.4	9.5 \pm 3.9	7.9 \pm 3.8	8.2 \pm 1.9
	GVM + NP	21.9 \pm 7.8	14.5 \pm 4.7	11.9 \pm 3.8	8.8 \pm 2.3	10.4 \pm 3.4
Platelet count ($10^9/l$)	ACM	195 \pm 75	154 \pm 60*	134 \pm 61*	116 \pm 69*	118 \pm 69*
	GVM + NP	255 \pm 99	232 \pm 82*	210 \pm 78*	210 \pm 73*	261 \pm 98*
C-reactive protein (mg/l)	ACM	1.3 \pm 2.7	3.2 \pm 2.0	5.3 \pm 3.8*	5.9 \pm 4.4*	5.8 \pm 4.0*
	GVM + NP	0.6 \pm 1.5	1.4 \pm 1.8	2.3 \pm 2.1*	3.3 \pm 2.3*	3.3 \pm 3.0*
Prothrombin time INR	ACM	1.83 \pm 0.5	1.86 \pm 0.5	1.74 \pm 0.5	1.46 \pm 0.4	1.25 \pm 0.2
	GVM + NP	2.11 \pm 0.7	1.75 \pm 0.5	1.59 \pm 0.8	1.30 \pm 0.3	1.18 \pm 0.3
Activated partial thromboplastin time ratio	ACM	2.02 \pm 1.0	1.98 \pm 0.6	1.98 \pm 0.6	1.92 \pm 0.6	1.63 \pm 0.3
	GVM + NP	1.81 \pm 0.5	1.65 \pm 0.4	1.73 \pm 0.7	1.59 \pm 0.6	1.38 \pm 0.4
Fibrinogen (mg/dl)	ACM	219 \pm 72	342 \pm 117	368 \pm 161	443 \pm 153	490 \pm 220
	GVM + NP	234 \pm 76	279 \pm 87	319 \pm 106	350 \pm 117	415 \pm 117
D-dimers (ng/ml)	ACM	2,238 \pm 928	1,069 \pm 874	384 \pm 279	288 \pm 208	423 \pm 391
	GVM + NP	2,402 \pm 510	649 \pm 478	696 \pm 531	729 \pm 690	228 \pm 213

Mean \pm SD.

AVM, auto control mode; GVM, gradient variable mode; INR, international normalized ratio; NP, nursing protocol.

* $P < 0.05$.

INR means International normalized ratio; BE means Base excess; MB is the name of the isoenzyme and it does not have to be expanded.

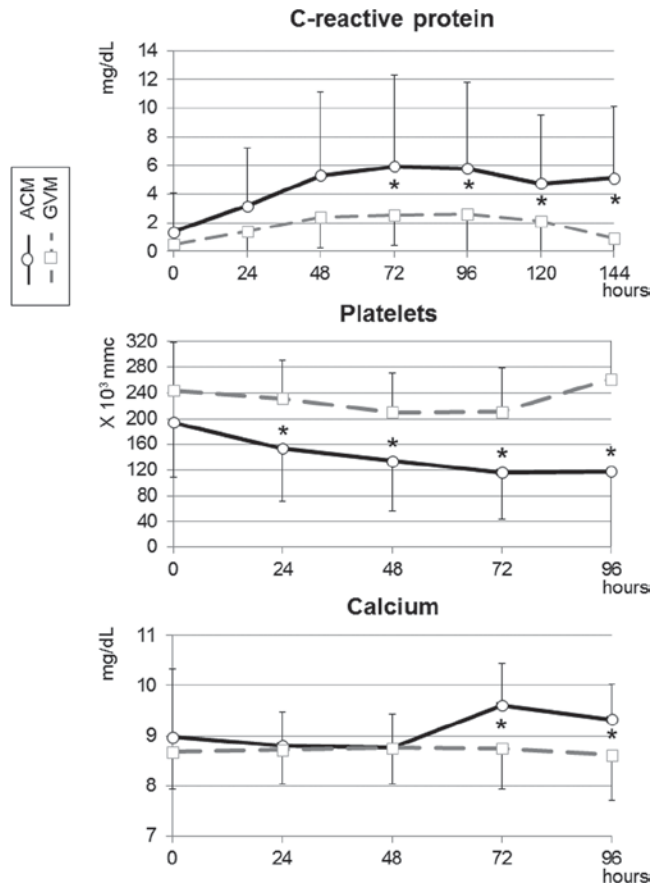


Figure 3. C-reactive protein level, platelet count, and calcium levels in hypothermic newborns treated with the “auto control mode” (ACM) or the “gradient variable mode” (GVM).

is believed to be caused by an excessive extra renal production of 1,25-dihydroxyvitamin D [17,33,34,36,38] by the granulomatous macrophages, as observed in other granulomatous inflammations, such as sarcoidosis [39] which increases the intestinal calcium uptake [20].

These complications were not detected in our patients. However, the comparison of values of C protein and calcemia showed significantly higher values in the group of newborns treated with the ACM mode and the platelet count was significantly lower in this group. We cannot exclude a bias due to the small sample size; however, such data could suggest a more pronounced skin inflammation in the group of newborns exposed to abrupt changes of temperature, even if SFN was only observed in two neonates. This suggestion is supported by the observation that these differences continued between the two groups even after the exclusion of the two infants with SFN.

In conclusion, the lower incidence of skin injuries and lower CRP and serum calcium levels in newborns treated with the GVM mode increases the suspicion that rapid changes in temperature may be harmful to infants. Further studies are recommended to confirm the benefits of hypothermia obtained in a more gentle mode associated with a NP with periodic mobilization.

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