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Cooled infants with encephalopathy: are heavier infants with weaker heart at a cutaneous disadvantage?

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Sub cutaneous fat necrosis of the newborn (SCFN) is a rare condition characterized by acute transient hypodermatitis that develops in the first few weeks of life predominantly in term infants (1) and presents as reddening of the skin and hardening of subcutaneous tissue particularly in the back, neck, thigh and bony prominences. Several predisposing factors for SCFN drawn mainly from small case series have been reported in the literature including maternal factors such as gestational diabetes, preeclampsia; ii] perinatal factors such as traumatic delivery, perinatal asphyxia, hypothermia and iii] neonatal factors such as thrombocytosis.(1) Since the introduction of therapeutic hypothermia (reducing core temperature to 33.5°C) as the standard of care for newborn infants with moderate to severe perinatal asphyxial encephalopathy, case reports of SCFN in therapeutically cooled infants with perinatal asphyxial encephalopathy(2, 3) and reports of SCFN from national registries of infants cooled for perinatal asphyxial encephalopathy have emerged.(4, 5) These suggest asphyxia and hypothermia as risk factors for SCFN. In this issue, Courteau et al have explored additional risk factors in cooled infants with perinatal asphyxial encephalopathy, which will be useful data for clinicians looking after cooled infants.(6)

Incidence

The incidence of SCFN in infants with perinatal asphyxial encephalopathy varies from 0.9% to 2.8%. (4, 5) Interestingly, the multi center randomized controlled trials of therapeutic hypothermia in infants with perinatal asphyxial encephalopathy that

have collectively recruited 763 infants between them reported only one infant with SCFN. (7-9) However, Courteau et al report an incidence of SCFN of 7% (95% CI: 4.3-11.3) occurring in the first two weeks of life (range 6-25 days of life) in their cohort. Is this because of increased awareness among clinicians, better recognition, different population of infants, different technique of cooling, misdiagnosis and frequent early neonatal follow-up providing opportunities for diagnosis unlike the randomized control trials where the infants were followed up after 18 months of age, when the potential window of diagnosis could have been missed?

This could be due to combination of all these factors. Publication of case reports of SCFN in cooled infants with encephalopathy might have certainly increased the awareness among clinicians aiding increased diagnosis. Nearly 27% of participants in the ICE trial (10) were from Canada and there were no reports of SCFN in the trial participants and consequently there is unlikely to be a population difference. The cooling technique has drifted more towards servo-control whole body cooling as described by Courteau et al compared to cool cap(9), manual whole body cooling(7, 8) and refrigerated gel packs(10) in the clinical trials. The servo-controlled devices alter the temperature of the coolant or water in the blanket between 4°C and 42°C to maintain target core temperature at 33.5°C.(6) Exposure of skin to the extreme low temperature may worsen the dermal vasoconstriction predisposing the adipose tissue to solidification resulting in SCFN. However in a small number of cooled infants (n=4) SCFN seems to occur independent of the cooling method, proportion of measured temperature outside the target range, implying the exposure of skin to extreme low temperature of the blanket remained comparable between infants with and without SCFN.(5) SCFN is diagnosed clinically and there is a potential to misdiagnose sclerema or scleroderma as SCFN although the former two occurs in sick premature infants in the first week of life and lacks fat necrosis in the histological

evaluation.(4) It is unknown whether regular follow-up visits in Courteau et al study enhanced the detection of SCFN.(6)

Macrosomia and haemodynamic instability

Courteau et al have reported in infants with SCFN as compared to infants without SCFN higher birth weight g, mean (SD), 4162(903) versus 3329(586); higher percentage of infants with birth weight \geq 90th centile, 60% versus 15%; higher body surface area m², mean (SD), 0.24(0.03) versus 0.22(0.02). In cooled infants whose birth weight was \geq 90th centile and had SCFN compared to the infants without SCFN, there was higher proportion of inotropic use (100% versus 53%), in particular use of epinephrine (56% versus 37%) and higher maximum troponin mcg/L, median (IQR), 2.79 (0.68; 12.59) versus 0.11 (0.08;0.52) albeit only 20-33% of infants in the two groups had their troponin measured. For every 100 g increase in body weight, the odds of SCFN increased by 1.2 (95% CI 1.1-1.3) independent of other risk factors.

Does this simply reflect that heavier babies were also sicker or do they have higher amount of fat being exposed to cold stress or do they have inherently different type of dermal fat or is their skin exposed to extremely lower temperature of the blanket for prolonged periods to maintain the core temperature within the target range given the larger surface of the body. Although infants with SCFN compared to infants without SCFN did not differ in the severity of asphyxia or encephalopathy, they had evidence of multiorgan impairment including cardiac and some suggestion of renal impairment. We do not currently know about the content and type of dermal fat in heavier infants and perhaps we may need to investigate the lowest blanket temperature and the temperature oscillations these infants are exposed to with servo-controlled cooling devices. Being aware of these risk factors will encourage clinicians to look out for SCFN while looking after the heavier babies and will aid

counseling parents of this potential complication. Interestingly this report shows that frequent change in posture during cooling does not preclude the occurrence of SCFN.

Certainly being heavier with a weaker heart puts the cooled infants at a cutaneous disadvantage, does this disadvantage extend to the brain as well? Fortunately and interestingly this is at odds with the brain and heavier cooled infants with birth weight $\geq 25^{\text{th}}$ centile have better outcomes of reduced death and severe neurodevelopmental disability compared to lighter infants with birth weight $\leq 25^{\text{th}}$ centile.(11)

Is SCFN a dangerous complication?

Although there are reports of hypercalcaemia occasionally associated with nephrocalcinosis (1, 4) and occasionally requiring treatment with diuretics to enhance calcium diuresis and corticosteroid and bisphosphonates to treat symptoms of hypercalcaemia such as vomiting and constipation, Courteau et al did not observe hypercalcaemia in their cohort of SCFN, but rather the lowest ionized calcium concentration was lower.(6) Platelet count was observed to be lower in infants with SCFN consistent with other reports. Occasionally there can be bleeding within the plaques leading to haematoma and requiring surgical intervention.(4) Courteau et al have not presented data about resolution of the SCFN lesions in their children. Reports suggest that SCFN is a fairly benign condition and is self-limiting with no superficial skin changes and may lead to subcutaneous atrophy observed by 32 months of age.(1)

Generalizability of the risk factors

SCFN being a rare condition, risk factors for SCFN derived from small case series and small cohorts may not necessarily apply to other populations. This is seen in Courteau et al's report where some maternal and perinatal risk factors such as diabetes and shoulder dystocia described in other small cohorts were not seen frequently in their cohort of SCFN. This in addition to the small event rate of SCFN may represent that we currently have well defined cohorts of infants with moderate to severe perinatal asphyxial encephalopathy who are exposed to mild hypothermia in a controlled manner unlike in previous reports. Given the rare incidence of SCFN, it is worthwhile to collect the data of incidence of SCFN and investigate these risk factors through larger national and international databases such as Neonatal Data Analysis Unit (NDAU), International Network for Evaluation of Outcomes (iNeo) and Vermont Oxford Network (VON).

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