ORIGINAL ARTICLE

Stridor in neonates with hypoxic-ischaemic encephalopathy subject to selective cerebral or whole body hypothermia

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Received 16 June 2015; accepted 14 October 2015
Available online 21 July 2016

KEYWORDS
Stridor; Hypothermia; Hypoxic-ischaemic encephalopathy

Abstract
Introduction: Hypothermia treatment has improved the prognosis of asphyxiated neonates. Widely used, it has demonstrated to be safe without severe side effects. The aim of this article is to review the incidence of stridor amongst asphyxiated newborns treated with hypothermia in our unit.

Methods: Retrospective chart review of our patients.

Results: Stridor was presented in 7/75 (9.3%) of patients during hypothermia. Three received whole body hypothermia, 3 selective cerebral, and in one case both techniques were used. All cases required increased respiratory support.

Conclusions: Different mechanisms may be responsible for the appearance of stridor in patients with hypoxic-ischaemic encephalopathy (HIE). In our series the incidence of stridor was similar for the two hypothermia devices. To better understand these possible side effects of hypothermia, further prospective studies (which should include laryngoscopy) are needed.

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Introduction

Hypoxic-ischaemic encephalopathy (HIE) is a major cause of neurologic injury in neonates. Its incidence in developed countries is of one to two cases per thousand live births.¹ The impact of hypoxic-ischaemic disease is significant in terms of both mortality and long-term morbidity, as 25% of those affected go on to have long-term neurodevelopmental sequelae.¹ Hypoxic-ischaemic encephalopathy is the cause of approximately 20% of cases of cerebral palsy in children.³ In the past decade, early cooling of the body temperature by 3–4°C initiated within 6 h of life and for 72 h, applied to the whole body or selectively to the head, has been shown to improve the outcomes of these patients, significantly reducing mortality and moderate to severe neurodevelopmental pathology at 18, 22 and 24 months with a number needed to treat of 6–7.¹,¹,⁴,⁵ Long-term follow-up studies have shown that this improvement is sustained.⁶,⁷ Review studies that have analysed the side effects of therapeutic hypothermia implemented in controlled intensive care unit settings by teams with extensive experience and training in the management of these patients have only found a significant increase of sinus bradycardia and thrombocytopenia, and no clinically significant adverse effects.¹,²,¹,⁴,⁸

A small-sample study of safety outcomes⁹ reported that stridor was more frequent in patients treated with whole body hypothermia, with an incidence of 29%, than in patients with HIE not treated with hypothermia (P = .01).

A more recent study¹⁰ reported five cases of stridor in patients treated with whole body hypothermia, which corresponded to an incidence of 9.6%.

In this study, we have reviewed the cases of stridor that developed in patients with HIE treated with whole-body or selective brain hypothermia.

Materials and methods

We conducted a descriptive retrospective study by analysing the medical records of all patients born at 36 or more weeks' gestation that received a diagnosis of hypoxic-ischaemic encephalopathy and were treated with active hypothermia in our hospital following the recommendations of the Sociedad Española de Neonatología (Spanish Society of Neonatology).¹¹ Our main criterion for initiating active hypothermia was the degree of clinical encephalopathy, assessed by the alertness of newborns with a history of risk factors in the perinatal period and clinical manifestations of neonatal pathology.

We included all patients found for the January 2010–December 2014 period, who amounted to 71. We excluded patients with airway malformations or primary neuromuscular disorders.

We obtained the approval of the Clinical Research and Ethics Committee prior to conducting the study.

Results

Between January 2010 and December 2014, a total of 71 patients born at 36 or more weeks' gestation underwent treatment with hypothermia for HIE, of whom 43 were treated with selective brain cooling and 28 with whole body hypothermia.

Seven newborns developed stridor during their stay, which corresponded to an incidence of 9.8%. Tables 1 and 2 describe the general characteristics of the patients and the treatment with hypothermia.

All of the patients had moderate encephalopathy except for case 3, who had severe encephalopathy, and case 7, who had mild-to-moderate HIE (we included this case because the patient had a significantly altered level of alertness).
### Table 1  Pregnancy and delivery characteristics.

<table>
<thead>
<tr>
<th>Case</th>
<th>GA</th>
<th>BW (g)</th>
<th>Sex</th>
<th>Pregnancy</th>
<th>Abnormal CTGR</th>
<th>Meconium in amniotic fluid</th>
<th>Type of delivery</th>
<th>Resuscitation step</th>
<th>1/5/10 min Apgar</th>
<th>Umbilical cord pH</th>
<th>Infectious comorbidity</th>
<th>Referred from another facility</th>
<th>HT during transport</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>40+4</td>
<td>2.280</td>
<td>F</td>
<td>Monitored, maternal diabetes</td>
<td>Yes</td>
<td>Yes</td>
<td>Emergency caesarean</td>
<td>IV</td>
<td>2/5/7</td>
<td>6.85</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>41+3</td>
<td>3.490</td>
<td>M</td>
<td>Monitored, maternal diabetes, hypothyroidism</td>
<td>No</td>
<td>Yes</td>
<td>Vacuum extraction</td>
<td>IV + massage</td>
<td>3/5/7</td>
<td>7.18</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>38+6</td>
<td>2.060</td>
<td>F</td>
<td>Monitored, maternal diabetes, hypertension</td>
<td>Yes</td>
<td>No</td>
<td>Emergency caesarean</td>
<td>IV</td>
<td>1/5/6</td>
<td>&lt;6.80</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
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<td>40+3</td>
<td>2.870</td>
<td>F</td>
<td>Monitored, normal</td>
<td>Yes</td>
<td>No</td>
<td>Emergency caesarean</td>
<td>III</td>
<td>7/9</td>
<td>6.99</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>39+3</td>
<td>3.250</td>
<td>M</td>
<td>Monitored, normal</td>
<td>Yes</td>
<td>No</td>
<td>Emergency caesarean</td>
<td>III</td>
<td>6/8</td>
<td>&lt;6.80</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>2.900</td>
<td>F</td>
<td>Monitored, normal</td>
<td>Yes</td>
<td>No</td>
<td>Forceps</td>
<td>IV</td>
<td>7/7</td>
<td>6.86</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>41+6</td>
<td>3.935</td>
<td>M</td>
<td>Monitored, normal</td>
<td>No</td>
<td>Yes</td>
<td>Vaginal CPAP</td>
<td>6/8</td>
<td>7.25</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**BW,** birth weight (g); **CPAP,** continuous positive airway pressure; **CTGR,** cardiothoracograph recording; **F,** female; **GA,** gestational age; **HT,** hypothermia; **M,** male.

### Table 2  Stridor characteristics.

<table>
<thead>
<tr>
<th>Case</th>
<th>Type of HT</th>
<th>IT</th>
<th>Difficulties with IT or accidental ET</th>
<th>ET (hours post birth)</th>
<th>Onset of stridor (hours post birth)</th>
<th>Phase</th>
<th>Min/max T</th>
<th>T at start of rewarming</th>
<th>T at onset of stridor</th>
<th>Treatment of stridor</th>
<th>Glycaemic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SB</td>
<td>Yes</td>
<td>No</td>
<td>7</td>
<td>87</td>
<td>R</td>
<td>33.2/35.3 °C</td>
<td>35.5 °C</td>
<td>35.8 °C</td>
<td>CPAP, Nebulised adrenaline</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>CT</td>
<td>Yes</td>
<td>No</td>
<td>&lt;1</td>
<td>14</td>
<td>M</td>
<td>32.8/34.2 °C</td>
<td>33.6 °C</td>
<td>35.8 °C</td>
<td>CPAP</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Both</td>
<td>Yes</td>
<td>No</td>
<td>55</td>
<td>116</td>
<td>R</td>
<td>32/34.1 °C</td>
<td>34.6 °C</td>
<td>35.8 °C</td>
<td>↑ FiO₂</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>SB</td>
<td>No</td>
<td></td>
<td>32</td>
<td>27</td>
<td>M</td>
<td>32.3/35.5 °C</td>
<td>33.8 °C</td>
<td>33.5 °C</td>
<td>CPAP</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>CT</td>
<td>No</td>
<td></td>
<td>32</td>
<td>27</td>
<td>M</td>
<td>32.3/33.9 °C</td>
<td>33.8 °C</td>
<td>33.5 °C</td>
<td>CPAP</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>SB</td>
<td>Yes</td>
<td>No</td>
<td>0.5</td>
<td>62</td>
<td>M</td>
<td>32.4/34.6 °C</td>
<td>33.8 °C</td>
<td>33.5 °C</td>
<td>CPAP</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>CT</td>
<td>No</td>
<td></td>
<td>82</td>
<td>R</td>
<td>33/34 °C</td>
<td>33.5 °C</td>
<td>35.7 °C</td>
<td>CPAP</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**CPAP,** continuous positive airway pressure; **ET,** extubation; **FiO₂,** fraction of inspired oxygen; **HT,** hypothermia; **IT,** intubation; **M,** maintenance; **R,** rewarming; **SB,** selective brain; **T,** temperature; **WB,** whole-body.
While their Apgar scores were relatively high, patients 4, 5 and 6 developed clear signs of nonreassuring foetal status (abnormal cardiotocograph, scalp blood pH < 7) and neonatal disease (all presented with clinical HIE with an altered level of alertness and cord blood pH < 7 or abnormal rhythms in EEG monitoring).

Patient 7 was referred by another facility due to features of moderate HIE and a history of meconium in amniotic fluid and nuchal cord, with no other apparent signs of foetal or neonatal pathology, but with a significantly altered level of alertness that persisted on arrival to our hospital, so that the passive hypothermia initiated at the referring hospital was continued with active hypothermia.

As for the hypothermia approach used in the described cases of stridor in our patients, we found no indication for or against either of the two methods (significant systemic involvement vs significant cranial haemorrhage or fracture), save for the availability of equipment and the preference of the neonatologist in charge.

All patients were given morphine hydrochloride for analgesia during therapeutic hypothermia. Tables 1 and 2 summarise the characteristics of the patients.

Case 1: the patient arrived at our hospital at 7 h post birth with a rectal temperature of 30.6 °C and underwent planned extubation to nasal CPAP, which was well tolerated; at 2 h, it was possible to discontinue CPAP with a maximum fraction of inspired oxygen (FiO₂) of 21%, in the absence of symptoms of stridor. Treatment with selective brain hypothermia was initiated at 9 h of life. Rewarming was initiated after 72 h of treatment, and it was during this phase that the patient developed inspiratory stridor with retractions and respiratory acidosis that required initiation of nasal CPAP with a maximum FiO₂ of 39% and administration of nebulised adrenaline. The symptoms of respiratory distress improved in a few hours, allowing for the reduction of FiO₂ to 21% nine hours after the onset of symptoms and discontinuation of CPAP at 31 h.

Case 2: the patient was transferred to our hospital following the onset of convulsive seizures. On arrival at 7 h post birth with a temperature of 38 °C the patient presented with symptoms of moderate HIE with convulsions, leading to initiation of active whole-body hypothermia. Six hours after initiation of hypothermia, at 14 h of life, the patient developed inspiratory stridor and respiratory distress requiring support with nasal CPAP with a maximum FiO₂ of 21% for 48 h, with subsequent resolution of the respiratory symptoms. The seizures were treated with levetiracetam and phenobarbital.

Case 3: active whole-body hypothermia was initiated at 4 h and 45 min post birth due to clinical features of severe encephalopathy with no trunk involvement. The patient was given phenobarbital and levetiracetam to treat convulsive seizures and received respiratory support with conventional mechanical ventilation with a maximum FiO₂ of 21%. Planned extubation to nasal CPAP was performed at 55 h of life, which the patient tolerated well. Sixty hours after extubation (116 h post birth), during the rewarming phase, the patient developed inspiratory stridor requiring an increase of the maximum pressure to 30%. The body temperature prior to the onset of stridor was 34.6 °C and had originally been 35.8 °C, at which time the patient had hypokalaemia (2.6 mmol/L) and hypernatraemia (147 mmol/L). The symptoms of stridor resolved after 48 h. In total, and due to the convulsive seizures, the patient remained under hypothermia for four days, which was switched from systemic cooling to selective brain cooling in the last 24 h due to malfunction of the whole-body hypothermia system.

Case 4: at the time of admission, the patient required noninvasive ventilation with nasal CPAP and a maximum FiO₂ of 40% due to respiratory distress without stridor that was discontinued at 6 h post birth. The patient was kept under passive hypothermia until 10 h post birth, when selective brain hypothermia was initiated due to the detection of abnormal electric discharges in the brain; the seizures were treated with levetiracetam. The patient developed inspiratory stridor with laboured breathing at 32 h of life, which required resuming ventilation with nasal CPAP at a maximum FiO₂ of 25%. The body temperature was 33.2 °C before stridor and 33.8 °C at the onset of stridor. The stridor resolved after 24 h, allowing the discontinuation of respiratory support.

Case 5: the patient was transferred to the neonatal unit from the maternity ward under nasal CPAP with a maximum FiO₂ of 30% and passive cooling. Active hypothermia was initiated at 3 h and 50 min post birth. At 17 h post birth, CPAP was switched to a maximum FiO₂ of 21% delivered through nasal prongs, which the patient tolerated well. The patient received levetiracetam starting at 12 h post birth due to the detection of abnormal electric discharges in the brain, which were asymptomatic. At 27 h post birth, the patient developed stridor and respiratory distress with acidosis (pH, 7.21; PaCO₂, 67 mmHg; HCO₃⁻, 26.8 mmol/L) and required resuming ventilatory support with nasal CPAP and a maximum FiO₂ of 21%, to which the patient responded well, with symptoms resolving within 12 h. The temperature measured one hour prior to the onset of stridor was 33.4 °C, and 33.5 °C at the onset. Rewarming started at 72 h and proceeded without complications.

Case 6: the patient had been under passive hypothermia since birth, and active hypothermia was initiated at 12 h of life. The patient developed inspiratory stridor with laboured breathing at 62 h post birth, requiring nasal CPAP with a maximum FiO₂ of 21%. The body temperature one hour prior to the onset of stridor was 33.2 °C, and 33.4 °C at the time of onset. The patient responded well to CPAP, which was discontinued 26 h from its initiation.

Case 7: the patient arrived with a body temperature of 34.3 °C and did not require respiratory support. Active hypothermia was initiated at 5 h and 45 min post birth without complications. Rewarming was initiated at 72 h from a temperature of 33.5 °C, and six hours later the patient developed inspiratory stridor and respiratory distress, requiring support with nasal CPAP with a FiO₂ of 21%. The patient responded well, and CPAP was discontinued after nine hours.

Discussion

We present seven cases of stridor in patients with HIE treated with hypothermia. Our study did not find an association between stridor and the hypothermia approach (whole-body or selective brain cooling), as we observed stridor in three patients treated with whole-body hypothermia,
three patients treated with selective brain hypothermia, and one patient treated with both. We also did not find an association between stridor and the phase of treatment, as three patients (42.8%) developed stridor during rewarming and four (57.2%) during maintenance. All patients but one required respiratory support with noninvasive ventilation, and symptoms resolved in less than 72 h in all patients.

While none of our patients required reintubation and mechanical ventilation, this was necessary in one of the five patients in the series published by Orme et al.\textsuperscript{10}

In our case series, only four of the seven patients (57.2%) required intubation in the maternity unit. All were extubated without complications and the onset of stridor occurred more than 13 h after extubation, so mechanisms other than the previous intubation may have been at play in the development of stridor.

Several mechanisms may be involved. Different types of receptors populate the laryngeal mucosa (chemoreceptors, mechanoreceptors) and they are known to stimulate the internal branch of the superior laryngeal nerve (afferent pathway), conveying information to the central nervous system through the solitary tract and then the ipsilateral nucleus ambiguous in the brainstem. Via the recurrent laryngeal nerve (efferent pathway), the motor neurons in this locus cause the bilateral contraction of the thyroarytenoid muscles, which pull the vocal ligament leading to closure of the larynx. The stimuli that trigger this reflex may be mechanical, chemical\textsuperscript{10} or thermal.

Temperature is one of the factors that have been associated in the literature with abnormalities in this reflex.\textsuperscript{13,14} Increases in body temperature may lower the threshold of the laryngeal closure reflex, which several authors have identified as one of the possible causes of apnoea and sudden death in febrile infants.\textsuperscript{15,16}

This confirmed previous findings of cold-sensitive receptors in the nasal/ethmoidal mucosa, as this type of receptors has been found in the ethmoidal mucosa of cats\textsuperscript{17,18} and dogs.\textsuperscript{19}

The mechanism of vocal fold abduction and adduction is complex and largely depends on a balance between the abductor (the posterior cricoarytenoid muscle) and adductor muscles (the other intrinsic laryngeal muscles). At the same time, the activity of these muscles depends on the innervation of the external branch of the superior laryngeal nerve and the recurrent laryngeal nerve, although the traditionally accepted patterns of innervation are increasingly disputed, with recent evidence confirming a considerable variability (interpersonal and even between hemilarynges in single individuals) in the motor supply from either nerve to different muscles.

Sensation to the supraglottis is supplied by the internal branch of the superior laryngeal nerve, which enters the larynx through the thyrohyoid membrane, while glottic and subglottic sensory innervation is provided by the recurrent laryngeal nerves.

Experiments conducted in dogs have demonstrated the depressive effect of cooling, which can reduce by up to 66% the activity of the posterior cricoarytenoid muscle, the only intrinsic laryngeal muscle that abducts the vocal folds, resulting in a reduction of glottal patency and the associated increased resistance to airflow. This muscle is mainly innervated by the recurrent laryngeal nerve, although, as mentioned above, it can also be innervated by the superior laryngeal nerve. The inhibitory effect of cooling on the posterior cricoarytenoid muscle does not take place following topical anaesthesia of the supraglottic mucosa or superior laryngeal nerve section,\textsuperscript{20} which suggests the presence of thermoreceptors in the supraglottis.

In an experimental study conducted on pigs, Wadie et al.\textsuperscript{21} analysed the glottal closing force under different core body temperature conditions. They concluded that the glottal closure reflex significantly increased with hyperthermia and decreased with hypothermia.

It follows that temperature may be a key mechanism in the development of stridor in these patients. In this regard, we should note that in a study conducted by Eicher et al.,\textsuperscript{9} the incidence of stridor was 29% and patients were ventilated with humidified air at 34 °C, while in our case series and the one presented by Orme et al.,\textsuperscript{10} patients received ventilation with humidified air at 36–37 °C, and the incidence of stridor was lower and nearly identical, of 9.8% and 9.6%, respectively. It would be interesting to find out about the approach to respiratory management and the incidence of stridor in other units that use hypothermia to assess the actual significance of these differences.

The other major mechanism that may be involved is upper airway oedema. Some publications suggest that the extracellular oedema that develops during hypothermia could lead to a reduction of the diameter of the upper respiratory tract, increasing resistance to airflow and giving rise to stridor. This effect would be very relevant in neonates, given the small calibre of their upper airway, especially in the subglottic region, where its diameter is smallest.

One of the main limitations of our study is its retrospective design, as we may have missed cases of stridor in our review of medical records. Another significant limitation is that laryngoscopy was not performed at the onset of stridor.

Conclusions

Different mechanisms may be at play in the development of stridor in patients with HIE treated with hypothermia. In our case series, we did not find an association with the type of active hypothermia used, or with the phase of treatment.

In the future, prospective studies using laryngoscopy could help improve our understanding of the pathophysiology of stridor in children treated with hypothermia, allowing for the implementation of preventive measures and the selection of the most effective treatment.

Conflict of interests

The authors have no conflict of interests to declare.

References