Health care costs during the first 20 years of life in infants with hypoxic-ischemic encephalopathy in Brazil: estimated economic benefits generated by the use of therapeutic hypothermia and brain monitoring

Gabriel Fernando Todeschi Variane, Alexandre Netto, Daniela Pereira Rodrigues, Danieli Mayumi Kimura Leandro, Carolina Nunes de França, Nathalie Sales Llaguno, Maurício Magalhães, Rafaela Fabri Rodrigues Pietrobom, Teresa Maria Lopes de Oliveira Uras Belém, Marcelo Jenné Mimica

Abstract

Background: Hypoxic-ischaemic encephalopathy (HIE) is a leading cause of long-term disability. Infants with HIE may require specific lifelong care, representing a devastating social and economic impact. Therapeutic hypothermia (TH) has been proven to be a safe and effective treatment; however, its potential economic impact associated with continuous electroencephalographic monitoring is still unknown in Brazil. This study aimed to evaluate the potential economic benefits provided by TH and continuous electroencephalographic monitoring in the first 20 years of life in infants with HIE in Brazil.

Methods: A resource utilization questionnaire about healthcare of infants with HIE was answered by 57 pediatricians and neonatologists in all five regions of Brazil. This data was used to calculate an annual weighted average of patient management costs according to the presence or degree of disability, considering only directly related health costs. A mathematical calculation was performed considering local incidence of HIE and the number of live births per year. Rates of death and survival for different levels of disability and the effect of TH on these outcomes were estimated from the two most relevant randomized controlled trials on TH.

Results: There was an approximately 26-fold increase in spending when the severe disability group was compared to the no disability group (p-value<0.0001, ANOVA-Bonferroni). The estimated total cost of patients with no disability, mild, moderate, and severe disability is US$ 6,808.53, US$ 32,208.43, US$ 105,791.78 and US$ 175,698.58, respectively, and the estimated costs related to the use of TH and neuromonitoring were estimated in US$ 2,824.00. Considering a weighted average between TOBY trial and NICHD trial, it is estimated annual savings of US$ 39,700,000-79,401,000.

Conclusions: This study estimated a significant increase in the costs associated with the degree of disability and a positive impact of TH throughout the first 20 years of life.

Keywords: Children with disability, Health care costs, Hypoxic-ischemic encephalopathy, Neonatal intensive care, Therapeutic hypothermia

terapêutica (HT) é comprovadamente um tratamento seguro e eficaz; entretanto, seu potencial impacto econômico associado ao monitoramento eletroencefalográfico contínuo ainda é desconhecido no Brasil. Este estudo tem como objetivo avaliar os potenciais benefícios econômicos proporcionados pela HT e pela monitorização eletroencefalográfica contínua nos primeiros 20 anos de vida em lactentes com EHI no Brasil. **Métodos:** Um questionário de utilização de recursos sobre cuidados de saúde de crianças com EHI foi respondido por 57 pediatras e neonatologistas das cinco regiões do Brasil. Esses dados foram usados para calcular uma média anual ponderada dos custos de cuidados de saúde destes pacientes de acordo com a presença ou grau de incapacidade, considerando apenas custos de saúde diretos. Um cálculo matemático foi realizado considerando a incidência local de EHI e o número de nascidos vivos por ano. As taxas de mortalidade e de sobrevivência para diferentes níveis de incapacidade e o efeito da HT nestes resultados foram estimados a partir dos dois ensaios clínicos randomizados e controlados mais relevantes sobre a HT. **Resultados:** Houve um aumento de aproximadamente 26 vezes nos gastos quando o grupo com deficiência grave foi comparado ao grupo sem deficiência (*p*-valor<0,0001, ANOVA-Bonferroni). O custo total estimado para os pacientes sem incapacidade, com incapacidade leve, moderada e grave é de US$ 6.808,53, US$ 32.208,43, US$ 105.791,78 e US$ 175.698,58, respectivamente, e os custos estimados relacionados ao uso da HT e da neuromonitoramento foram estimados em US$ 2.824,00. Considerando uma média ponderada entre o estudo TOBY e o estudo NICHD, estima-se uma economia anual de US$ 39.700.000-79.401.000. **Conclusões:** Este estudo estimou um aumento significativo dos custos associados ao grau de incapacidade e um impacto positivo da HT ao longo dos primeiros 20 anos de vida.

**Palavras-chave:** Crianças com deficiência, Custos de cuidados de saúde, Encefalopatia hipóxica-isquêmica, Terapia intensiva neonatal, Hipotermia induzida

**Introduction**

![Table 1](image)

<table>
<thead>
<tr>
<th>Degree of disability</th>
<th>Hypothermia (%)</th>
<th>Clinical trials results</th>
<th>Mean (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TOBY</td>
<td>NICHD</td>
<td>Normothermia (%)</td>
</tr>
<tr>
<td>Death</td>
<td>29</td>
<td>27.8</td>
<td>30</td>
</tr>
<tr>
<td>Severe</td>
<td>14</td>
<td>16.7</td>
<td>24</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>18.8</td>
<td>13</td>
</tr>
<tr>
<td>Mild</td>
<td>10</td>
<td>24.6</td>
<td>18</td>
</tr>
<tr>
<td>No disability</td>
<td>68</td>
<td>40.6</td>
<td>45</td>
</tr>
</tbody>
</table>

*Among survivals

During the neonatal period, multiple conditions are associated with increased risks of death or long-term disability. Perinatal asphyxia is the third most common cause of neonatal death (23%) worldwide(1-3). In Brazil, it accounts for approximately 7% of all deaths between 0 and 6 days after birth, with wide variation between areas within the country (2.6% to 16%) (4). Perinatal asphyxia can lead to hypoxic-ischemic encephalopathy (HIE), which affects between one to two cases in 1000 live births in high-income countries and five to ten cases per 1000 live births in low-middle income countries (LMIC)(1-3,5-10).

In survivals, HIE can lead to long-term disability(11-13), including cerebral palsy, cognitive delay, memory impairment, visual dysfunction, and learning problems(11-13). These infants may require specific lifelong care, representing a devastating social and economic impact. In the United States, the estimated overall life costs of children with disabilities is around US$ 67 billion(14). Furthermore, disabled individuals and their families are more likely to experience economic and social disadvantages(15).

For the last 15 years, therapeutic hypothermia (TH) has become the standard of care for neuroprotection in infants with moderate or severe HIE(16,17) since the results of several randomized controlled trials demonstrated a significant reduction in neonatal mortality and neurodevelopmental impairment(12,13,16-18). Summarized data of the largest trials are presented in Table 1(12,13). In those trials, a high incidence of seizures was observed, which can be completely subclinical, requiring, as a critical part of the management, an accurate assessment of cerebral background activity and prompt recognition of seizures by using continuous electroencephalography (cEEG) with or without amplitude-integrated electroencephalography (aEEG)(19-23).

Even though TH has been proven to be a safe
and effective treatment for HIE\(^{12,13,15,16}\), the potential economic impact of this treatment associated with continuous electroencephalographic monitoring is still unknown in Brazil.

Therefore, the objectives of this study are to estimate the health care costs associated with disability along the first 20 years of life in HIE infants in Brazil and the potential economic benefits provided by treatment with TH and continuous electroencephalographic monitoring.

**Materials and Methods**

**Study design**

A panel discussion with three neonatologists with expertise in neonatal follow-up was organized followed by a literature review on treatment guidelines for infants with neurological sequelae using Medline and Lilacs databases, including articles published until July 2021. Based on this literature review, four possible long-term outcomes for infants with HIE were used specifically for this study:

a) No disability: normal life without additional burden to the health care system.

b) Mild disability: learning and mild cognitive impairment, speech delay, mild visual or hearing impairment. Patients are not subject to social and economic dependence and demand small life-long medical costs.

c) Moderate disability: motor, learning and swallowing moderate difficulties, speech delay, visual and/or hearing deficits. Often, require specialized follow-up with speech therapy, physiotherapy, occupational therapist, neurologist, orthopedist, and dentist. There is social and economic dependence throughout life. Patients may have activities but hardly develop their full economic potential.

d) Severe disability: severe swallowing difficulties (gastrostomy) and/or breathing difficulty (home oxygen and/or tracheostomy). Severe motor (cerebral palsy) and cognitive disabilities and are dependent on their caregivers for life. Problems with vision and/or hearing. Multidisciplinary follow-up is extensive, involving specialties such as pediatrics, neurology, neurosurgery, pediatric surgery, orthopedics, ophthalmology, otolaryngology, physiotherapy, speech therapy, occupational therapy, and other possible specialties. There is often a need for high-cost special medications. The number of hospitalizations requiring Pediatric Intensive Care Unit and surgery is higher compared to children without or with mild or moderate disabilities. These children need specialized care, schools, transport, and social assistance. Thus, there is a high dependence on the healthcare system.

A resource utilization questionnaire was developed in Google Forms for each age group: one to 12 months; >one to ten years; and 11 to 20 years, and considering the presence and levels of disability. The questionnaire included questions about the average cost and time per medical/non-medical appointment, number of medical consultations or health care professional sessions needed, number of complementary exams, medications, procedures, complications, services, and support materials. (Supplementary file 1).

Pediatricians and neonatologists with experience in managing infants with HIE were invited to answer this questionnaire. These professionals were from all five regions of Brazil, and were included by convenience sampling based on the availability to answer the questionnaire. Answers were tabulated to define patterns of resource utilization for the four possible levels.

**Cost estimate**

An annual weighted average of patient management costs according to the presence or degree of disability was calculated to define the estimated economic benefits provided by adequate treatment for infants with HIE in Brazil. Only directly related health costs were considered using the Supplementary Health System as a paying source. The values of all identified health cost items were determined using official databases of the Brazilian Hierarchical Classification of Medical Procedures from 2016 (CBHPM, 2016)\(^24\), which was most commonly applied for hospital billing by the time this study was performed, and information obtained from the questionnaires. For this study, only the post-Neonatal intensive care unit (NICU) discharge costs were included.

The health costs were also stratified into different age groups and classified as follows:

**Direct costs**

Cost of medical and non-medical consultations: pediatrician, neurologist, neurosurgeon, orthopedist, general/pediatric surgeon, ophthalmologist, otolaryngologist, physiotherapy, speech therapy, and occupational therapy.

Number of medical and non-medical consultations: pediatrician, neurologist, neurosurgeon, orthopedist, general/pediatric surgeon, ophthalmologist, otolaryngologist, physiotherapist, speech therapist, and occupational therapist.

Number of laboratory exams: complete blood count, glucose, urea, creatinine, sodium, potassium, coagulogram.

Number of other complementary exams: pelvic
panoramic radiography, foot radiography, spine radiography, chest radiography, chest computed tomography, skull computed tomography, skull magnetic resonance imaging, electroencephalogram, electrocardiogram.

- Medications: antibiotics, anti-seizure medications, and analgesics.
- Complications: pneumonia, fracture, pressure sores, hip surgery, scoliosis surgery.
- Procedures: tenotomy, gastrostomy, fundoplication, tracheostomy, botox.
- Support services and material: orthosis/prosthesis, hospital bed, wheelchair, toilet chair, enteral diet, supplemental oxygen, home care.

Medical and non-medical consultation costs were calculated based on the Time-Driven Activity-Based Costing (TDABC) method\(^{(20)}\), which considers the consultation costs per hour. The questionnaires’ answers were also contemplated to define these costs. Thus, the final estimated cost was the mean value between the TDABC method and the questionnaire answers.

Laboratory exam costs included blood count, glycemia, urea, creatinine, sodium, potassium, and coagulogram. Other complementary exams comprised radiographic studies (hip, feet, spine, chest), skull tomography, magnetic resonance imaging, electroencephalogram, and electrocardiogram. Furthermore, the participants answered questions related to the use of medications, complications, procedures, support services, and materials. There were three options of answers: “very unlikely”, “likely” and “very likely”. The costs of laboratory exams, complementary exams, and procedures were estimated based on the CBHPM, 2016\(^{(24)}\). Medications and complications were also calculated within the three options of answers.

The cost of TH treatment using a servo-controlled temperature management system was defined based on recommendations of the manufacturer. Estimation of the equipment cost included a useful life of five years and usage on two neonates per month. Continuous electrographic brain monitoring cost was estimated from the CBHPM (2016)\(^{(24)}\). The electrographic brain monitoring costs were based on a mean monitoring period of 96 hours. Since previous data did not report a significant change in length of stay, costs related to hospitalizations in the NICU were not included in this analysis. In fact, the NICHD trial reported a slightly, but not significant, decrease in length of stay in the population treated with TH\(^{(26)}\).

To estimate the potential reduction in costs over a 20-year period for HIE infants treated with TH vs no treatment, a mathematical calculation was performed considering the incidence of HIE in LMIC\(^{(10)}\) of five to ten per 1,000 live births and three million live birth per year in Brazil, which would provide an absolute number of infants between 15,000 to 30,000 thousand per year. Rates of survival without disabilities, or with mild, moderate, or severe disabilities or death and the effect of TH on these outcomes were calculated based on the mean obtained from the childhood outcomes observed on TOBY and NICHD trials\(^{(12-13)}\). The overall estimated cost for TH during NICU stay was derived from CBHPM (2016)\(^{(24)}\). All costs were calculated in Brazilian currency (BRL) and converted into American dollars (US$) in 2020. When the study was conducted, US$ 1.00 was equivalent to BRL 4.55.

Statistical analysis

Resource utilization items and their costs were grouped by type in a Microsoft Excel® spreadsheet. Each item was estimated based on the survey data and presented as median. The costs were calculated based on the survey data, CBHPM 2016\(^{(24)}\) and TDABC method\(^{(20)}\), and they were presented as mean. Continuous variables are presented as means and/or medians and categorical variables as frequencies and percentages. The Kolmogorov-Smirnov test was used for examining the normality of continuous variables. ANOVA-Bonferroni test was used for comparison between the levels of disability. A p-Value of less than 0.05 was considered significant (pre-Bonferroni). All analyses were made using Statistical Package for Social Science® version 22.0 software.

Results

The questionnaire was sent to 64 pediatricians from all five Brazilian regions. Fifty-seven (89%) answered: 25 (44%) from the Northeast, 25 (44%) Southeast, tree (6%) South, two (3%) North, and two (3%) Midwest.

The estimated costs associated with medical and non-medical consultations are presented in Figure 1. Over a 20 years period, these costs were significantly different between presence and levels of disability (p-Value<0.0001, ANOVA with Bonferroni post hoc):

- a) No disability - medical: US$ 4,127.52 and nonmedical: US$ 0;
- b) Mild disability - medical: US$ 9,164.27 and nonmedical: US$ 8,791.28;
- c) Moderate disability - medical: US$ 14,266.26 and nonmedical: US$ 56,364.12;

The laboratory and complementary exams estimated costs are presented in Figure 2. A significant difference was observed between presence and levels of disability (p-Value<0.0001, ANOVA with Bonferroni post hoc):

- a) No disability - laboratory: US$ 326.04 and noncomplementary: US$ 326.04;

Figure 3 shows the estimated total direct costs according to the level of disability, and Table 2 shows the estimated total direct costs according to the level of disability by age group. There was an approximately 25.81-fold increase in spending when the severe disability group was compared to the without disability group (p-Value<0.0001, ANOVA Test, Bonferroni post hoc test):
- Without disability - estimated total costs: US$ 6,808.53.
- Mild disability - estimated total costs: US$ 32,208.43.
- Moderate disability - estimated total costs: US$ 105,791.78.
- Severe disability - estimated total costs: US$ 175,698.58.

The estimated costs related to the use of TH and neuromonitoring are shown in Table 3: Equipment=US$ 40,000.00; useful life=five years; considering two neonates per month; costs per patient=US$ 333.33. Electrographic brain monitoring costs=96 hours; costs per hour=US$ 41.6; the first two hours correspond to 100% of the value and the other 94 hours equivalent to 70% of the costs; total=US$ 2,824.00. The estimated direct costs of long-term care of infants that received TH in the neonatal period and its details concerning the three age groups evaluated (one to 12 months, one to ten years, and 11 to 20 years) are presented in Supplementary Tables - Files 2-9.

The weighted average impact of implementation of TH according to the TOBY and NICHD trials in the incidence of death and disability was calculated and displayed in Table 1. According to those results, the impact of TH was estimated in a reduction of 9% on death and, among survivors, a reduction of 9% on severe, 0.1% on moderate and 2% on mild disabilities and an increase of 10.8% in the number of patients
Our study used a panel of experts and a TDABC approach, together with review of the literature to estimate the cost of children with disabilities related to HIE. A significant difference in estimated costs among different types of disabilities was determined. Children with severe disabilities had a 26-fold increase in direct healthcare costs when compared to children without disabilities. A significant reduction of total estimated costs for children with major disabilities in the country, when using TH and continuous EEG, resulted in potential savings ranging from 39 to 79 million dollars.

The high economic burden of children with disabilities in our study, agrees with published literature. In 2003, the Research Triangle Institute (RTI) International and the Centers for Disease Control and Prevention (CDC)\textsuperscript{(14)} in the United States estimated the direct and indirect economic costs associated with developmental disabilities, defined as chronic conditions that cause harm to physical, mental, cognitive, speech, language, and self-care\textsuperscript{(14)}. The average lifetime cost per person was estimated at US$ 1,014,000.00 for mental retardation, US$ 921,000.00 for cerebral palsy, US$ 41,700.00 for decreased hearing acuity, and US$ 56,600.00 for decreased visual acuity. It is noteworthy that the indirect costs with these patients corresponded to the highest percentage with an average of 63-81%. Total direct cost was approximately US$ 12.3 billion for mental retardation, US$ 2.2 billion for cerebral palsy, US$ 770 million for decreased hearing acuity, and US$ 570 million for decreased visual acuity. Total direct costs accounted for 42 to 82% of each disability\textsuperscript{(14)}.

A study conducted by Kruse et al, 2009\textsuperscript{(27)} estimated a higher lifetime cost of € 800,000.00 for individuals with cerebral palsy. In all categories, the costs with cerebral palsy were higher. Health and social costs were higher in children than in adults, and the highest

### Table 2

<table>
<thead>
<tr>
<th>Age group</th>
<th>1–12 months</th>
<th>1–10 years</th>
<th>11–20 years</th>
<th>Total estimated costs over 20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without disability</td>
<td>771.63</td>
<td>3868.00</td>
<td>2168.90</td>
<td>6808.53</td>
</tr>
<tr>
<td>Mild Disability</td>
<td>2186.38</td>
<td>16172.13</td>
<td>13849.92</td>
<td>32208.43</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>6376.92</td>
<td>52695.25</td>
<td>46719.61</td>
<td>105791.78</td>
</tr>
<tr>
<td>Severe Disability</td>
<td>7843.89</td>
<td>81016.04</td>
<td>86838.65</td>
<td>175698.58</td>
</tr>
</tbody>
</table>

The estimation included medical and nonmedical consultations, laboratory and complementary exams. There were significant differences after comparison between the levels of disability, in both cases (ANOVA Test, Bonferroni post hoc test, p-Value<0.0001).
Estimated impact on death and costs in children with disability of implementation of therapeutic hypothermia in a populational level considering the weighted average between the TOBY and NICHD trials\(^{(12,13)}\).

<table>
<thead>
<tr>
<th>Total infants with HIE (n)</th>
<th>Outcome</th>
<th>Estimated percentage (%)(^{a})</th>
<th>Normothermia (n)</th>
<th>Estimated percentage (%)(^b)</th>
<th>Hypothermia (n)</th>
<th>Estimated impact (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>37</td>
<td>5,550 – 11,100</td>
<td>28.4</td>
<td>4,260 – 8,520</td>
<td>-1,290 – -2,580</td>
</tr>
<tr>
<td></td>
<td>Severe disability</td>
<td>24.5</td>
<td>2,315 – 4,631</td>
<td>15.3</td>
<td>1,643 – 3,286</td>
<td>-672 – -1,344</td>
</tr>
<tr>
<td></td>
<td>Moderate disability</td>
<td>13.5</td>
<td>1,276 – 2,552</td>
<td>13.4</td>
<td>1,439 – 2,878</td>
<td>163 – 327</td>
</tr>
<tr>
<td></td>
<td>Mild disability</td>
<td>19</td>
<td>1,796 – 3,591</td>
<td>17.3</td>
<td>1,858 – 3,716</td>
<td>63 – 125</td>
</tr>
<tr>
<td></td>
<td>No disability</td>
<td>43.5</td>
<td>4,111 – 8,222</td>
<td>54.3</td>
<td>5,832 – 11,664</td>
<td>1,720 – 3,442</td>
</tr>
<tr>
<td>Cost (Thousand US$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>627,568 – 1,255,136</td>
<td></td>
<td>540,512 - 1,081,025</td>
<td></td>
<td>87,055 - 174,111</td>
</tr>
</tbody>
</table>

\(^{a}\)Estimated percentage calculated in Table 1.

Table 5

Total estimated savings with the implementation of therapeutic hypothermia and continuous EEG considering the weighted average between the results from the TOBY and the NICHD trials.\(^{(12,13)}\)

| Reduction of cost with decreasing disability rates (thousand US$) | 87,055 – 174,111 |
| Estimated cost of adequate treatment\(^a\) (thousand US$)         | 47,355 – 94,710  |
| Total estimated savings (thousand US$)                            | 39,700 – 79,401  |

\(^{a}\)Values of therapeutic hypothermia were estimated by summing values of standard therapeutic hypothermia treatment and continuous electroencephalography.\(^{(21)}\)

In conclusion, although several studies show the benefits of TH among newborns with HIE, it is important to better describe this disease’s potential economic burden in a middle-income country setting. This study estimated a significant increase in the costs associated with the degree of disability. Adequate treatment with TH reduces the number of infants with moderate and severe HIE in Brazil. Our study used a panel of experts from all regions of the country to decrease the disparity of heterogeneity of care among distant locations. The TDABC methodology was used to evaluate the costs of children with disabilities. Although this is not the standard methodology to perform cost-effectiveness analyses, in order to evaluate potential social and economic improvement provided by a new intervention, this methodology was used due to resource constraints and the lack of data in this field. Our estimates considered direct healthcare costs, but costs of intensive care unit readmissions (also direct) and indirect costs such as loss of productivity and parents’ mental healthcare were not included in this analysis. Therefore, savings from implementing treatment for infants with HIE on a large scale are potentially much greater.

Table 4

<table>
<thead>
<tr>
<th>Total infants with HIE (n)</th>
<th>Outcome</th>
<th>Estimated percentage (%)(^a)</th>
<th>Normothermia (n)</th>
<th>Estimated percentage (%)(^b)</th>
<th>Hypothermia (n)</th>
<th>Estimated impact (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Death</td>
<td>37</td>
<td>5,550 – 11,100</td>
<td>28.4</td>
<td>4,260 – 8,520</td>
<td>-1,290 – -2,580</td>
</tr>
<tr>
<td></td>
<td>Severe disability</td>
<td>24.5</td>
<td>2,315 – 4,631</td>
<td>15.3</td>
<td>1,643 – 3,286</td>
<td>-672 – -1,344</td>
</tr>
<tr>
<td></td>
<td>Moderate disability</td>
<td>13.5</td>
<td>1,276 – 2,552</td>
<td>13.4</td>
<td>1,439 – 2,878</td>
<td>163 – 327</td>
</tr>
<tr>
<td></td>
<td>Mild disability</td>
<td>19</td>
<td>1,796 – 3,591</td>
<td>17.3</td>
<td>1,858 – 3,716</td>
<td>63 – 125</td>
</tr>
<tr>
<td></td>
<td>No disability</td>
<td>43.5</td>
<td>4,111 – 8,222</td>
<td>54.3</td>
<td>5,832 – 11,664</td>
<td>1,720 – 3,442</td>
</tr>
<tr>
<td>Cost (Thousand US$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>627,568 – 1,255,136</td>
<td></td>
<td>540,512 - 1,081,025</td>
<td></td>
<td>87,055 - 174,111</td>
</tr>
</tbody>
</table>

\(^{a}\)Estimated percentage calculated in Table 1.

**Note:** Estimated equipment costs were in neonatal care and specialized education. Some cost items were not considered, including household care expenses and adverse effects on the parents’ physical and mental health. In the United Kingdom, it is estimated that £ 5 million is spent on care and services required by children with cerebral palsy and severe eating and learning difficulties.

In agreement with previous data, our study also suggested that implementing adequate treatment to infants with HIE is cost-effective. In 2010, Regier et al, 2010\(^{(29)}\) reported the cost-effectiveness based on outcomes published in the three major randomized trials of infants with moderate or severe encephalopathy treated with TH. The cost-effectiveness of neonatal TH increased at 18 years after birth, and the probability of being cost-effective was 95%. When examining cost-effectiveness acceptability curves, the probability that TH was cost-effective was 52 to 69%, differing from an analysis by the United Kingdom cooling records. The likelihood of TH being cost-effective was very high, between 92 and 96%. This evidence further supported the adoption of TH in clinical practice. A recent study evaluated the cost-effectiveness of cooling compared to no cooling infants with severe HIE\(^{(30)}\). The results showed that cooling is cost-effective and improves the quality-adjusted life years (QALYs) and outcomes, although the authors found an increase in the costs.

To our knowledge this is the first cost analysis of the effect of using TH for infants with moderate or severe HIE in Brazil. Our study used a panel of experts from all regions of the country to decrease the disparity of heterogeneity of care among distant locations. The TDABC methodology was used to evaluate the costs of children with disabilities. Although this is not the standard methodology to perform cost-effectiveness analyses, in order to evaluate potential social and economic improvement provided by a new intervention, this methodology was used due to resource constraints and the lack of data in this field. Our estimates considered direct healthcare costs, but costs of intensive care unit readmissions (also direct) and indirect costs such as loss of productivity and parents’ mental healthcare were not included in this analysis. Therefore, savings from implementing treatment for infants with HIE on a large scale are potentially much greater.
severe disabilities leading to a significant reduction of the estimated total direct costs with healthcare throughout the first 20 years of life.

**Funding:** None

**Declaration of interest:** G.F.T.V. and A.N. are founders of Protecting Brains and Saving Futures Organization, a company that provides continuous neuromonitoring with electroencephalogram to high-risk infants. D.M.K.L., R.F.P.P., M.M., M.J.M. are employees at Protecting Brains and Saving Futures Organization and D.P.R., C.N.F., N.S.L. were employees at Protecting Brains and Saving Futures Organization during the development of this manuscript. T.M.L.O.U.B. does not report competing interests.

**Authors’ contributions:** All authors are responsible for the stages of the article

**References**


Article received: October 26, 2023
Article approved: May 15, 2024
Article published: June 6, 2024

**Responsible Editor**: Prof. Dr. Eitan Naaman Berezin (Editor-in-Chief).