“INDUCED THERAPEUTICAL HYPOTHERMIA IN CHILDREN AFTER TRAUMATIC BRAIN INJURY“

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1. SUMMARY

Sofía Gómez de la Cruz Pérez

**Induced hypothermia in children after brain trauma**

*Research aim:* The aim of this study is to analyze the beneficial effect of therapeutic hypothermia in children after brain trauma and what parameters are more concerning for future trials to be performed.

The objective of this systematic review is to evaluate which method of induced hypothermia should be studied in future trials by comparison of safety, mortality rate and outcomes of previous performed studies of mild and moderate induced hypothermia.

*Methodology:* Through the use of scientific databases (Ovid, Clinicaltrials.gov, Embase, Pubmed) 8 studies about induced hypothermia in children after brain trauma trials were selected for this systematic review, preferably within the past ten years, but some studies that exceed the ten year period have been included because of their clinical relevance in the subject.

*Study participants:* The study participants reviewed in this study is 493 (n=493) excluding participants of systematic reviews.

*Research results:* Moderate hypothermia induced early for 24 h followed by rapid rewarming is not safe and increases mortality, but this might be prevented using a different approach by longer period of cooling and slower rewarming. Still moderate hypothermia for 48-72h with slow rewarming did not seemed to improve outcomes or be safe. Mild hypothermia for 48h with slow rewarming achieve better results in preventing complications and outcomes, and moreover, it seemed to be safe.

*Conclusions:* Induced hypothermia appears to have beneficial effects treatment of traumatic brain injury (TBI), the method that gave better results was mild hypothermia for 48h with slow rewarming rate but further studies are needed to shape up a correct protocol of action.

*Recommendations:* Although the study of hypothermia remains controversial, I would suggest to continue with the investigations with mild hypothermia always under a clinical trial.

*Conflict of interest:* The author reports no conflicts of interest.
2. ABBREVIATIONS:

1. **CK-BB**: Brain specific Creatinine Kinase
2. **CNS**: Central Nervous System
3. **CSF**: Cerebro Spinal Fluid
4. **GCS**: Glasgow Coma Scale
5. **GOS**: Glasgow Outcome Scale
6. **HYPO**: hypothermic
7. **ICP**: Intracranial pressure
8. **NORMO**: Normothermic
9. **NSE**: Neuron specific enolase
10. **PCPC**: Pediatric Cerebral Performance Category
11. **TBI**: Traumatic brain injury
3. INTRODUCTION:

Traumatic brain injury (TBI) is the leading cause of traumatic mortality and disability in children and young people [1]. Different studies try to approach medical therapies towards diminishing adverse events and outcome caused by TBI. Despite the big efforts to minimize these outcomes, one third of the survivors will develop important neurological sequelae [2].

Therapeutic induced hypothermia (TIH) is known to have neuroprotective effect. Hypothermia is not only used in treatment of TBI, it has been also seen in cases of cardiac arrest, stroke or neonatal hypoxia, among others.[3] However, the use of TIH in TBI remains controversial because of lack of evidence of favorable results and safety.

The correct protocol for performance of hypothermia induction remains inconclusive, different techniques for cooling, time of induction of hypothermia, duration of hypothermia and rewarming remain under examination for better approach.

Different sources name stages of hypothermia in different wide ranges, this study will be focused on moderate hypothermia ranges of 32-33°C and mild hypothermia of 33-34°C.

Analysis of different trials using moderate and mild hypothermia in children are presented in this systematic review.

Despite the neuroprotective effects of hypothermia, it is associated with a number of potential adverse events that increase as body core temperature decreases, such as increase in arrhythmias, coagulopathies, electrolyte disturbances and infections among others. These may result in increased mortality rate and poor outcomes, resulting in lost of beneficial effect.

In this study, all of these adverse event, as well as outcomes and survival of patients of the studies selected, are analyzed in order to assess which method should be used to achieve better results and what parameters are more concerning during the treatment with hypothermia. With the data collection this study would assess the beneficial effect of therapeutic hypothermia in children after TBI.
4. AIM AND OBJECTIVES:

The aim of this study is to assess the beneficial effect of therapeutic induced hypothermia in children after brain trauma and what parameters are more concerning for future trials to be performed.

The objectives of this systematic review are:

1. To compare safety, mortality rate and outcomes of previous performed studies of mild and moderate induced hypothermia.

2. To determine some predictors for poor outcome after TBI.

3. To discuss which method of hypothermia (moderate versus mild) would be most preferable studied in future trials.
5. LITERATURE REVIEW

Traumatic brain injury is characterized by an early primary damage at the time of the lesion, that is caused by the forces of trauma itself; subsequently, alteration of normal biochemical reactions and activation of inflammatory processes, both systemically and intracranial, cause a secondary damage which evolves from hours to days. This secondary damage mechanism is not fully understood, but overall of reactions compromise neurological status by reduced oxygen and metabolite delivery and reduced clearance of metabolic waste and toxins. The increase of intracranial pressure (ICP), cerebral blood flow autoregulation disturbances, proinflammatory mediators and free radicals may lead to cerebral ischemia and cell death.[2][4][5].

Hypothermia is known to have neuroprotective properties which may alleviate the effects of secondary damage. This may be related to the decreased in all metabolic rate, cerebral blood flow, release of excitatory neurotransmitters, apoptosis, cerebral edema and cytokine response, however the exact mechanism is not fully understood. [3], it may even attenuate oxidative stress after TBI.

Hypothermia can be divided into mild (34-35.9 degree C), moderate (32-33.9 degree C), moderate deep (30.1-31.9) and deep (<30 degree C) mainly. It is associated with a number of potential adverse events, which increases as body core temperature decreases, thus it is believed that the safest temperature targets would be mild and moderate hypothermia.

Induced hypothermia is divided into three phases: induction (which can be started in the hospital or prehospital), maintenance and rewarming. Induction phase should be started very early to minimize neurological damage. Rewarming phase should be down slow to prevent adverse events such as rebound of ICP.

Other events to take under consideration include cardiac arrhythmias, coagulopathies, hypokalemia and infections which are the most important hypothermia-related complications during the cooling phase. The risk of these events increases with the lower temperatures. [14]
The study and monitoring these adverse events is indispensable for prevention and treatment of complications.

The analysis of different parameters that seem to be relevant during hypothermia is very helpful for better understanding of its role during traumatic brain therapy.

For evaluation of outcomes most studies use the five-category-assessment Glasgow Outcome Scale (GOS): 1, death; 2, vegetative state; 3, severe disability; 4, moderate disability; 5, good recovery. A GOS score of 4–5 is considered as a favorable/good neurological outcome, while a GOS score of 1–3 is unfavorable/poor outcome.[15]

Another functional outcome measure that is currently used is the Pediatric Cerebral Performance Category (PCPC) [23] which is a six-point scale: 1, normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, persistent vegetative state; 6, death.

Different studies focus on the study of poor outcomes predictors which is essential for a correct approach performance, such as:

- Increased intracranial pressure (ICP) is the major cause of death in TBI and predictor of poor outcome[6][7]. Pediatric guidelines refer that increase of ICP (<20mm Hg) is associated with poor outcomes in children after severe brain trauma, thus by monitoring ICP, survival rate and outcomes will improve. In older children and adults, normal ICP is 5-15mmHg compared to 2-4mmHg in infants and young children, however infants with open fontanelles may be able to accommodate slow increases of intracranial volume. [8]

- Hypotension within the first 6 h after trauma (early hypotension) may be a very useful predictor for poor outcome. Early hypotension defined as systolic blood pressure (SBP) < 5th percentile for age[9] is a better predictor for poor outcome than delayed hypotension or the use of SBP < 90 mmHg [10], some studies even determine that hypotension might be predictable for mortality [11].
The study of different biomarkers may be useful to determine progression of brain damage, assess primary brain injury and secondary insults.[12]

- Neuron specific endolase (NSE) is mainly located in the neurons and neuroectodermal cells, and its concentration in serum, or more important cerebrospinal fluid (CSF) is highly related with the degree of cell damage in the central nervous system (CNS) [13].

- Brain specific Creatinine Kinase (CK-BB) predominates in brain tissue and it increases after injury, and may be used a biomarker predictor for brain damage.

- S-100 serum levels also correlates with neurological damage, however its used as biochemical marker is controversial because it is also present in other tissues and it can be altered in cases of trauma patient without head injuries.[11]

- Some studies suggest that highly oxidizable polyunsaturated fatty acids levels in cerebro spinal fluid resulting from oxidative stress caused after TBI are related with outcome of these patients. This might be alleviated by hypothermia which might preserve antioxidant defenses of the patient. [16]
6. RESEARCH METHODOLOGY AND METHODS

Induced hypothermia has been studied for many years for different purposes due to its clear beneficial effects in neuroprotection, still, its clinical use in TBI still inconclusive.

This is a literature review of different studies that are focused on the study of induced hypothermia therapy in patients after TBI. Studies have been selected by searching in different scientific data bases (Pubmed, Clinicaltrials.gov, Ovid Medline, Embase), focusing in paediatric studies during the past 10 years (2007-2017), although search was extended to previous years studies due to their clinical relevance in the development of these studies. Studies in adult patients have been excluded, except for theoretical documentation.

Research was performed initially by using key words: induced hypothermia, brain injury, and trauma. Later on search was narrow to more specific areas by using also key words: paediatric, child, moderate hypothermia, mild hypothermia.

Initially both adults and paediatric patients were selected. Adult studies were excluded for analysis but some of them where used for clinical documentation. Studies for paediatric patient that suffered head trauma where selected and those that did not used induced hypothermia therapy were excluded. From these studies, only studies with inclusion criteria of Glasgow Coma Scale (GCS) less than 8 were selected.

Thus total sample of the study comprises 493 patients. Then, from these studies the analysis was divided in sections:

1. Studies that used inducted moderate hypothermia, which include 6 studies with a total sample of 441 children.

2. Studies that used inducted mild hypothermia, which include 2 studies with a total sample of 52 children.

Analysis of the studies was focussed on determine its safety, complications and outcomes of patients during treatment. Special attention was put to assess physiological effect of hypothermia in order to establish possible outcome predictors after TBI. Each trial compared hypothermic induced patients to normothermic patients, what help this study to compare under the same circumstances the beneficial or adverse effects of the treatment.
7. RESULTS AND THEIR DISCUSSION

The main aim of the study is, by comparison of hypothermic with normothermic patients benefits and adverse events, analyze safety of the treatment, as well as predictive factors for outcomes. The studies are represented in table 1 (see Table 1 below). It summarizes the main characteristics of the trials, their results and conclusion which will shape this study.

**Moderate hypothermia induction** was performed in all studies except for Grinkeviciute et al.[2] study that used mild hypothermia and Li H et al. which performed localized mild brain hypothermia [22]. What is more, the studies also differs in the time of action of each phase of hypothermia therapy:

Hutchinson et al.[21] proposed a short time of cooling started within 8 h and maintained for 24 h with rapid rate of rewarming, which presented more unfavorable outcomes in hypothermic (HYPO) groups, increasing rate of mortality (21%), thus safety could not be assessed.

On the other hand, early beginning of induction, for a longer period (48/72h) with slow rewarming rate was performed by Adelson et al.[17], Beca et al.[19], Li H et al. [22] with better results in mortality suggesting it may decrease mortality rate. However, these studies remain inconclusive due to the small sample sizes.

Then Adelson et al.[18] performed another study where they found no differences in outcomes and complications development between groups, what made them decided to stop the trial.

**Mild hypothermia** used by Grinkeviciute et al. [2] started whiting 6 h after trauma for 48 h, followed by slow rewarming achieve favorable outcome in 66% of the patients. Mortality rate was decreased and the therapy was safe.

**ICP** was decreased during the cooling phase considerably in all studies, however, some of them, mostly in the trials that used moderate hypothermia, there was an increase of ICP (>20 mmHg) during and after rewarming overwhelming the protective effects. This increase in ICP was highyrelatedwiththeprogressionofpooroutcomes.
Adelson et al. [18] proposed in its protocol to continue cooling phase for 24 more hours in cases that ICP increases at 48 h.

In the case of mild hypothermia therapy by Grinkeviciute et al. [2] and Li H et al. [22] ICP rebound was not as remarkable as in moderate hypothermia studies.

**Hypotension** episodes occurred in several studies, but they were easily manageable so difference between groups was not significant, in the case of Grinkeviciute et al. [2] or Beca et al.[19]

However Hutchinson et al. [24] presented in 2010 a post hoc analysis of his previous trial related to the impact of hypotension and low Cerebral Perfusion Pressure (CPP) on outcomes in children after severe TBI. They determined that the HYPO group presented more episodes of hypotension and low systolic blood pressures from 4 to 72 h than NORM group. CPP was significantly higher from 8 to 12 h in HYPO group and significantly lower from 32 to 60 h.

The result analysis showed that the relationship between patients with 1 or more episodes of hypotension or low CPP from 25-72 h in HYPO group was associated with poor outcome, but no during the first 24 h. In NORM group the presence of either episodes was associated with poor outcome in both time intervals.

**CSF biomarkers** study assessed by Li H et al. [22], conclude that hypothermia decreased the amount of NSE, CK-BB and S-100 after treatment. These biomarkers are helpful for outcome prediction after TBI, and support the protective effect of hypothermia in the Central Nervous System.

Other parameters to take under consideration include cardiac arrhythmias, electrolyte disturbances and infections. These parameters are affected directly by hypothermia, which increases its prevalence.

Bourdageset al.[20] studied the prevalence of cardiac arrhythmias in cases of TBI, and conclude that they are common and might be increased by hypothermia. Cardiac arrhythmias where present in other studies as well in both HYPO and NORMO groups [2], slightly increased in HYPO group but difference was not significant, and were easily manageable.
Table 1. Analysis of studies using induced moderate hypothermia, its main characteristics, the results of hypothermia groups compared to normothermia groups and conclusions from studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Characteristics</th>
<th>Results and Conclusions</th>
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<tbody>
<tr>
<td>3. Adelson et al. (2013)</td>
<td>Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids)</td>
<td>Starting of hypothermia induction: &lt;6 h Duration of hypothermia therapy: 48-72 h Rewarming: 0.5-1.0°C per 12-24 hour. * if at 48 h after rewarming ICP &gt;20</td>
<td>Total sample: 75 children</td>
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<tr>
<td><strong>Primary outcome</strong></td>
<td><strong>During hypothermia, HYPO presented lower heart rate, higher mean glucose level, lower platelet count, and prothrombin significantly higher between 25-72 h.</strong></td>
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<td>Mortality: was</td>
<td><strong>Unfavorable outcomes were higher in HYPO after rewarming rebound ICP occurred as well as increased hypotension episodes and lower cerebral perfusion pressures</strong></td>
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<td>decreased</td>
<td><strong>Mortality was higher (21%) in hypothermic than normothermic (12%).</strong></td>
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<td>Complications and</td>
<td><strong>Primary outcome PCPC was higher in normothermic on 12 months after injury.</strong></td>
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<td>outcomes:</td>
<td><strong>Long term visual memory significantly worst than normo. No other neurocognitive differences.</strong></td>
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<td>No differences with</td>
<td><strong>No differences in outcomes and complications within groups.</strong></td>
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<td>respect of</td>
<td><strong>No difference in primary outcome mortality.</strong></td>
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<td>coagulopathies,</td>
<td><strong>No differences in neurocognitive development (good and poor outcomes) at 3 month after injury.</strong></td>
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<td>infections,</td>
<td><strong>There is no significant differences in complications, outcomes in 12 month or primary outcome PCPC.</strong></td>
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<td>hypotension or</td>
<td><strong>However, it is important to highlight that rebound occurred in 54% of children, and systemic hypotension was also greater (17%) than in NORMO patients.</strong></td>
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<td>electrolite</td>
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<td>cardiac arrythmias</td>
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<td>ICP reduction on</td>
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<td>the first 72 h but</td>
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<td>remarkable increase</td>
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<td>Neurocognitive</td>
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<td>improvement:</td>
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<td>Functional status</td>
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<td>HYPO patients</td>
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<td>between 3 and 6</td>
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<td>months.</td>
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| RESULTS OF HYPOTHERMIC (HYPO) GROUP COMPARED TO NORMOTHERM (NORMO) GROUP |
| CONCLUSIONS | The use of hypothermia appears to be safe despite some complications such as arrythmias that were manageable and the rebound in ICP which may be avoided by decreasing rate of rewarming. It may also improve functional outcome. Further investigations are needed. | They conclude that this method is not safe, it does not present any beneficial effect on secondary outcomes, including functional or neurocognitive. In fact, it increases mortality. | The trial was stopped after analyzing safety results from other randomized trial [22] and the lack of evidence of the beneficial effect of hypothermia over normothermia in its own trial. | They conclude that this method of hypothermia may be safe, however it showed not improvement in outcome. |
Table 2. Analysis of studies using inducted mild hypothermia, its main characteristics, the results of hypothermia groups compared to normothermia groups and conclusions from studies.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CHARACTERISTICS</th>
<th>RESULTS OF HYPOTHERMIC (HYPO) GROUP COMPARED TO NORMOTHERMIC (NORMO) GROUP</th>
<th>CONCLUSIONS</th>
</tr>
</thead>
</table>
*Significance of intracranial pressure and cerebral perfusion pressure in severe pediatric traumatic* | **Totalsample:**  
- 30 children with TBI  
- 10 children with posthypoxic brain injury.  
**Starting of hypothermia induction** within 6 h.  
**Duration of hypothermia therapy:** 48 h.  
**Rewarming** passively 1°C each 4 h. | Intracranial pressure tend to be lower in patients with hypothermia  
CSF biochemical markers:  
- NSE was lower after treatment in HYPO group  
- CK-BB was also lower in hypothermia groups as 24, 48 and 72 h.  
- S-100 was also lower after therapy.  
Mortality was lower in HYPO group (8.3%) than NORMO group (20%).  
Follow up of the patient for recording of clinical information was not performed in this study. | They conclude that this method with mild hypothermia may be safe and showed improvements in neurological outcomes in children without increasing unfavourable events. |
| 2. Li H et al.(2008)  
*Protective effect of moderate hypothermia on severe traumatic brain injury in children.* | **Totalsample:** 22 children (12 with hypothermia)  
**Starting of hypothermia induction** within 8 h  
**Duration of hypothermia therapy:** 72 h  
**Rewarming** passively 1°C each 4 h | Mortality was lower in HYPO group (8.3%) than NORMO group (20%).  
Follow up of the patient for recording of clinical information was not performed in this study. | Determination of these neurological biomarkers levels can be used to determine possible prognostic outcomes.  
Hypothermia therapy was safe with no additionally complications. Benefitial effects were reflected in the decrease of ICP in the cooling phase and the decrease in biomarkers for poor prognosis. |
Table 3. Analysis of studies related to outcome prediction determinators, its main results

<table>
<thead>
<tr>
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<th>Study Reference</th>
<th>Study Title</th>
<th>Main Results</th>
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<tr>
<td>2.</td>
<td>Hutchinson et al. (2010)</td>
<td><em>Impact of Hypotension and Low Cerebral Perfusion Pressure on Outcomes in Children Treated with Hypothermia Therapy following Severe Traumatic Brain Injury: A post hoc Analysis of the Hypothermia Pediatric Head Injury Trial</em></td>
<td>Hypothermia group presented more episodes of hypotension and low systolic blood pressures. Cerebral Perfusion Pressure (CPP) was significantly higher from 8 to 12 h in hypothermia group and significantly lower from 32 to 60 h.</td>
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<tr>
<td>3.</td>
<td>Bourdages et al. (2010)</td>
<td><em>Cardiac arrhythmias associated with severe TBI and hypothermia therapy</em></td>
<td>Results in hypothermia group: - No significant differences in adverse events, complications or outcomes. - However, rebound of ICP and hypotension episodes were increased in hypothermia group.</td>
</tr>
</tbody>
</table>

**Characteristics**

**Results of Hypothermic (Hypo) Group Compared to Normothermic (Normo) Group**

**Conclusions**

1. The study of different biomarkers may be useful to determine progression of brain damage, assess primary brain injury and secondary insults.
2. However, poor outcome related to hypotension or low CPP in hypothermia occurred mostly when episodes took place after the first 24 h. In normothermia the presence of either episodes was associated with poor outcome in both time intervals.
3. Arrhythmias are common during hypothermia induction.
4. Hypothermia may be safe despite the adverse events.
5. No significant difference in mortality.
6. No improvement on outcome.

**Total Sample**: 16 children

- Moderate hypothermia, started within 8 h for 24 h.
8. CONCLUSIONS:

1) This study cannot assess the safety of hypothermia due to variety of results obtained in the different trials, however, mild hypothermia seems to be safer than moderate hypothermia. Mortality rate and poor outcome were higher in most of the studies that used moderate hypothermia. On the other hand, mild hypothermia induction decreased mortality rate and poor outcome.

2) Different parameters appear to be highly associated with poor outcome prediction. Major outcome predictors seemed to be hypotension episodes and ICP elevations, mainly after cooling phases. Other associated parameter may include low CPP episodes during and after rewarming phases.

This study also supports the use of neurological damage biomarkers levels in CSF such as of NSE, CK-BB and S-100 as outcome predictors. They appeared in lower amounts after therapy with hypothermia.

3) After study of both moderate and mild hypothermia trials and comparison of results of safety, mortality and outcome, the most preferable method of hypothermia seemed to be mild hypothermia for 48h with slow rewarming, it seemed to be safe and effective in preventing adverse event and improving outcomes, however further studies are needed to compare the results of this method in a larger sample.
9. PRACTICAL RECOMMENDATIONS:

Assembling of the data from different sources is very important for understanding the risk that decreased body core temperature brings and how to manage it.

The analysis of these studies made clear that and short aggressive approach of treatment is neither a safe or efficient way to perform it; thus short inducted hypothermia for 24h and rapid rewarming should be avoided, due to increase in complications and mortality rate.

The good results from the studies of Grinkeviciute et al. [2] and Li H. et al. [22] support the beneficial effect of hypothermia in neuroprotection and the approach of hypothermia appears to be safer and more efficient than those from moderate hypothermia. In addition, continuous monitoring of the patients during treatment is mandatory, this will help to collect data for analysis and both to prevent and treat adverse events of the treatment that usually occur, such as cardiac arrhythmias, hypotension episodes, increases in intracranial pressure, infections, etc. These adverse events are more prominent at lower temperatures, that is why mild hypothermia presented less adverse event during its therapy, than moderate.

However, further studies need to be performed to corroborate these hypothesis and put together the essentials for a proper protocol action.
10. LITERATURE LIST:


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*TH preserves antioxidant defenses after severe traumatic brain injury* Crit Care Med 2009 Vol. 37, No. 2


