Hypothermia in Intensive Care Unit

Definition

* **Hypothermia**: A state (regardless of cause) where the core body temperature is <36℃.(1)
* **Therapeutic hypothermia**: Hypothermia which is induced for a therapeutic purpose keeping in mind the possible side effects and control measures of it i.e. shivering.
* **Prophylactic hypothermia**: Hypothermia is called “Prophylactic” if it is administered early after injury (i.e head injury) and prior to increase in intra cranial pressure. (2)
* **Therapeutic normothermia :** Regulating the core body temperature in patient with fever in a range of 36-37.5℃ keeping in mind the possible side effects and control measures of it i.e. shivering. (1,3)
* The degree of therapeutic hypothermia can mild (34.0-35.9℃), moderate (32.0-33.9℃), moderately deep (30.0-31.9℃) or deep (<30.0℃). (1,2)

Physiological changes with injury to brain and role of hypothermia

The post insult phase after ischemia/injury to brain can be divided in to-

* Acute phase
* Sub-acute phase
* Chronic phase

**ACUTE PHASE**

Causes reverse transport of “GLUTAMATE”(6)

Attenuates “GLUTAMATE RECEPTOR” expression (Suppresses NMDA receptor phosphorylation.

)

↓regulates “ASTROCYTIC GLUTAMATE TRANSPORTER-1”

Release of Excitatory AA & Glutamate(4)

Cerebral ischemia/injury

↓ ATP due to ischemia

Permanent state of "NEURONAL HYPER-EXCITATION”(5)

Prolonged "GLUTAMATE" exposure

↓ ATP due to ischemia

Disruption of normal ion gradient & ↑ Ca+2 influx

↑ IC Ca+2, K+, NO synthesis, Reactive Oxygen Species

Mitochondrial dysfunction

Neuronal Injury & Death(5)

Prevents glutamate induced “NO synthesis”

**SUBACUTE PHASE**

**Decreased astrocyte & Microglia activation(7,8)**

Inflammation(4)

Activation of Glia cells, Microglia cells, Astrocytes, Leukocyte infiltration

Mediators

IL-1,6,18, TNF-α, Complement activation(9)

Decreases H2O2 level upto 50 times(5)

HYPOTHERMIA

**Decreased expression of inflammatory cytokines(10)**

**Decreases pro-apoptotic mediators**

**Increases Anti-apoptotic mediators(11,12)**

**Increases expression of P53 and enhances tissue repair(11)**

Apoptosis(4,5)

Pro-apoptotic mediators- Bcl-2 (B-cell lymphoma-2 associated) X protein, Fas, Caspase-3, Cytochrome-c

**Prevents activation of “METALLOPROTEINASE”**

**Augments expression of endogenous “METALLOPRROTEINASE INHIBITORS” (4)**

Disruption of Blood-Brain-Barrier(7)

Ischemic reperfusion

Traumatic injury

Mannitol Therapy

**Decreased NO synthesis & Decreased Aquaporin-4 chanel expression (4)**

Cerebral Edema

↑NO- ↑Vascular permeability

↑Aquaporin-4 chanel expression- ↑Cellular edema

There is no conclusive evidence that suggest that hypothermia has any role in chronic phase leading to neurological modelling and outcome. It comprises of gliogenesis and angiogenesis.

**CHRONIC PHASE**

APPLICATION OF HYPOTHERMIA

As described above hypothermia can be prophylactic or therapeutic. We will enlist the different indications for hypothermia first and then distinguish each indication for application of prophylactic or therapeutic hypothermia.

**Indications: -**

* Post cardiac arrest with poor neurological recovery
* Traumatic brain injury and ↑ICP (Prophylactic & Therapeutic hypothermia)
* Stroke
* SAH/ICH
* Spinal Cord Injury
* Hepatic encephalopathy associated with Acute Liver Failure
* Neonatal Encephalopathy due to birth Asphyxia

**Literature review:**

**Randomized trials**

Clifton etal conducted three successive trials 1993,2001,2011 to evaluate prophylactic hypothermia (32-33℃) vs normothermia in sever traumatic brain injury.

Clifton etal 1993:- (12)

46 patients randomized to hypothermia {32-33℃ vs normothermia instituted within 6 hours of non-penetrating head injury (GCS4-7)}. 48 hours after the core temp. was reached active rewarming started.

Seizure incidence was less, sepsis was more common, demonstrated better neurological outcome compared to normothermia.

Clifton etal 2001:- (13)

Multicentre, randomized, controlled trial. Included 392 patients and enrolled to hypothermia (33℃) or normothermia for 48 hours. There was no difference in outcome variables which included mortality and neurological outcome. The studied recommended to start hypothermia as soon as possible on arrival and they demonstrated a poor outcome in patients who arrived hypothermic and then enrolled into the normothermic group with early active rewarming.

Clifton etal 2011:- (14)

This was more organized, multicentre, randomized trial involving 97 patients in which patients were enrolled within 2.5 hours of admission. The study was stopped prematurely due to futility of intervention on interim analysis. There was no difference in mortality or neurological outcome between the two groups. Subgroup analysis demonstrated that prophylactic hypothermia had a better outcome when applied to patients who had surgical evacuation of hematoma. Unique to this study, patients in the hypothermia group displayed higher ICPs than patients in the normothermia group.

Aibiki etal in 2000 reported in a randomized controlled trial with 26 patients. The intervention group was cooled to 32-33 °C for 4-9 days. They demonstrated a significant mortality benefit (6.7% vs 27.3 %) and a better neurological outcome in the hypothermia group. A similar trial in the same year by Jiang etal included 87 patients and the intervention arm was cooled to 33-35°C. They demonstrated a better survival and neurological outcome in the intervention group. Marion eta l in 1997 published their study involving 197 patients and demonstrated a better neurological outcome at 3 months (Better Glasgow outcome scale GOS 38 vs 17%) in the intervention group. The subgroup analysis showed a better outcome with a GCS of 5-7 rather than <5. A more recent trial (2005) by Qiu etal reported similar mortality and neurological outcome benefit at 2 years with prophylactic s

qwtx6 days rather than1-3 days. They did not report any increase in complications with increased duration of hypothermia. Liu etal in 206 reported no difference in outcome with selective brain cooling to moderate hypothermia but the outcome was poor with normothermia.

**Reviews and Meta-analysis**

Crossley etal in their meta-analysis in 2014, include twenty trials with 1885 patients out of which 18 reported mortality outcomes. They reported a significant reduction in mortality relative risk=1.31, 95% CI 1.13-1.52, p=0.0004), I2 24%, no evidence of statistical heterogeneity). When studies with lower risk bias were included (14 studies) hypothermia was associated with significant mortality benefit (RR=1.62, 95% CI= 1.30-2.01, p<0.0001). Hypothermia was associated with significant improvement with neurological outcome (p<0.00001). Incidence of pneumonia was evaluated by 12 trials in 689 patients. Hypothermia did not increase the incidence of pneumonia but the data concluded to have statistical heterogeneity (I2=46%). The obvious flaw in this meta-analysis was the inclusion of studies which include studies from 1993 to 2011. The management strategies of head injury have changed a lot since 1993 and the meta-analysis may not represent the current patient population and practices.

BTF summary: -

The BTF evaluated studies published earlier and post 2007 in their new guidelines 4rth edition 2016. They considered ONE class I study and EIGHT class II study to compare Hypothermia to Normothermia. The guideline provides a Class IIB recommendation for prophylactic hypothermia in TBI.

* *Early (within 2.5 hours), short-term (48 hours post-injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury. 12*

**Eurotherm3235 Trial**

This was a multicenter (47 out of planned 55 centers recruited patients, majority (53%) happened in UK) European trial. Outcome assessors were blinded. Aimed at recruiting 600 patients with a power of 80% aiming at 9% reduction in unfavorable outcome. The initial sample size calculated was 1800 but the pilot study found a higher rate of unfavorable outcome in raised ICP group, thereby modifying the sample size to 600. Inclusion criteria included adult patients with closed head injury (no more than 10days old) and sustained ICP (>29mm Hg) for at least 5 mins in spite of all stage 1 treatment measures.

Stage-I measures included

Sedation, mechanical ventilation, head up >30 degrees, IV fluids with or without inotropes to maintain a MAP>80 mm Hg. Ventriculostomy with or without removal of CSF and surgical removal of space occupying lesions were optional. The core body temperature on enrollment had to be >36°C.

Intervention group- If there is sustained raised ICP in spite of stage I therapy, then patient subjected to therapeutic hypothermia. If he/she failed, then additional stage II followed by stage III therapy if required. Control group did not receive TH else managed similarly.

Stage II measures: - mannitol; hypertonic saline; inotropes to maintain cerebral perfusion pressure of >60mmHg

Stage III measures: - barbiturate therapy with processed EEG monitoring; decompressive craniectomy further surgical intervention if required

Rewarming was done once ICP was controlled 0.25°C per hour.

Extended Glasgow outcome score (GOS-E) at 6 months were worse with hypothermia (25.7 vs 36.5%, NNH 10). There was loss of follow-up with 10 patients but the study had a fragility index of 3 i.e if 3 patients in hypothermia had a good outcome instead of bad then the outcome would have been statistically insignificant or not harmful.

6-month mortality was significantly higher in hypothermia group, no difference in incidence of decompressive craniectomy, length of ICU stay, incidence of pneumonia. They reported more serious adverse events with hypothermia group 33 vs 10 events)

The authors concluded therapeutic hypothermia plus standard care for raised ICP in TBI did not result in improved outcome. The obvious limitations of the trial were early termination bias and lost outcome data of 10 patients.

**ANZICS POLAR trial (Prophylactic hypOthermia to Lessen trAumatic bRain injury)**

6 hospitals in (Alfred, Royal Perth, Princess Alexndra, Aukland, Gold Coast) and 3 pre-hospital agencies (Ambulance Victoria, St John WA, Queensland Ambulance) in ANZ and 4 sites on France, Bern in Switzerland, Riyadh in Saudi Arabia and AIIMS in India are participating.

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