ACCC 2019 Acute Critical Care Conference

The Korean Society of Critical Care Medicine

REVIEW: HYPOTHERMIA FOR MALIGNANT INCREASED INTRACRANIAL PRESSURE

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INTRACRANIAL PRESSURE

- Skull = ‘closed box’ Total Volume ; 1900ml
- 3 volume components

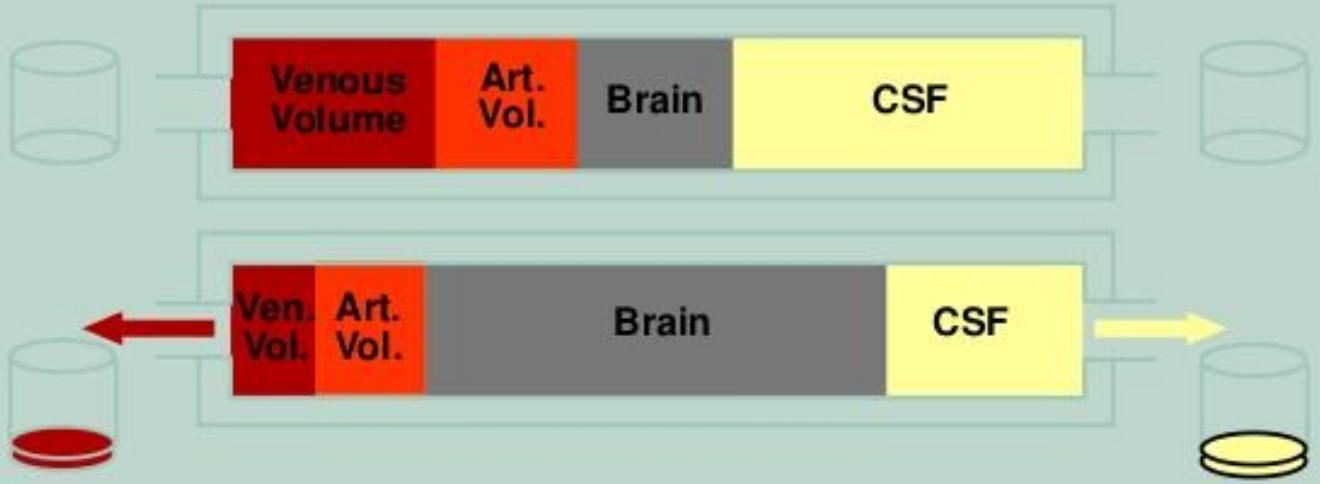
1.Brain Parenchyme	1300ml
IC space(1100ml) + EC space(200ml)	
2.Blood	60ml
3.Cerebrospinal fluid	140ml

- Each of the 3 componets contributes ICP(Monro-Kerlly Doctrin)
- Normal ICP ; 10~15mmHg

3 COMPONENTS OF INTRACRANIAL PRESSURE

Intracranial Hypertension in FHF

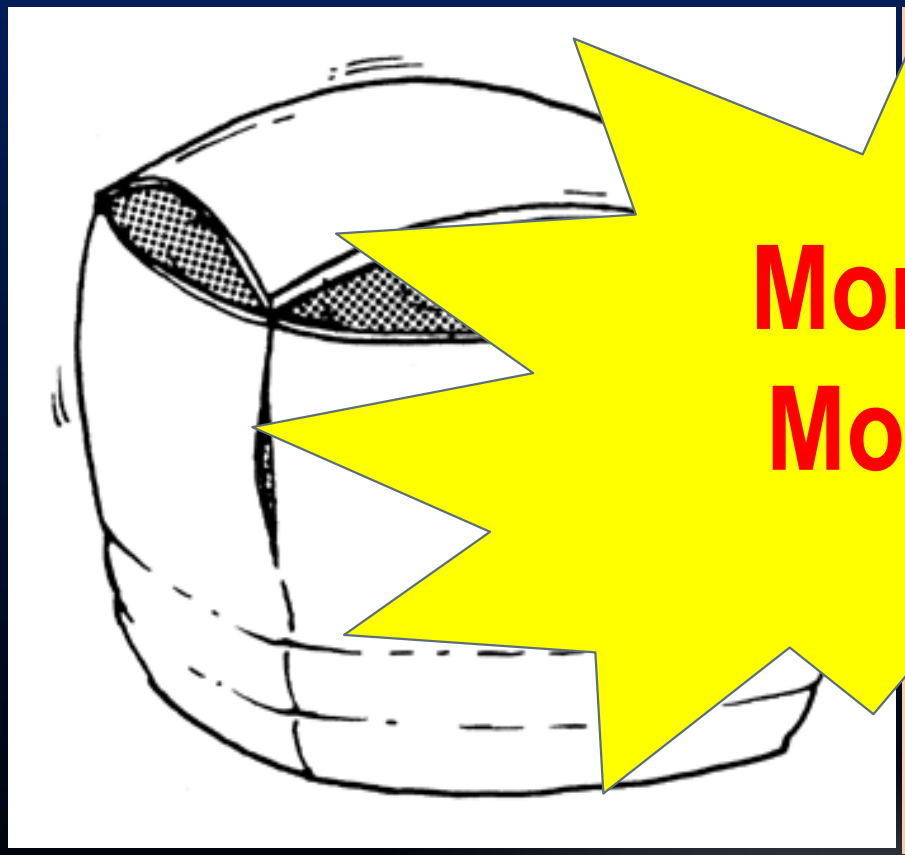
Monro-Kellie Doctrine

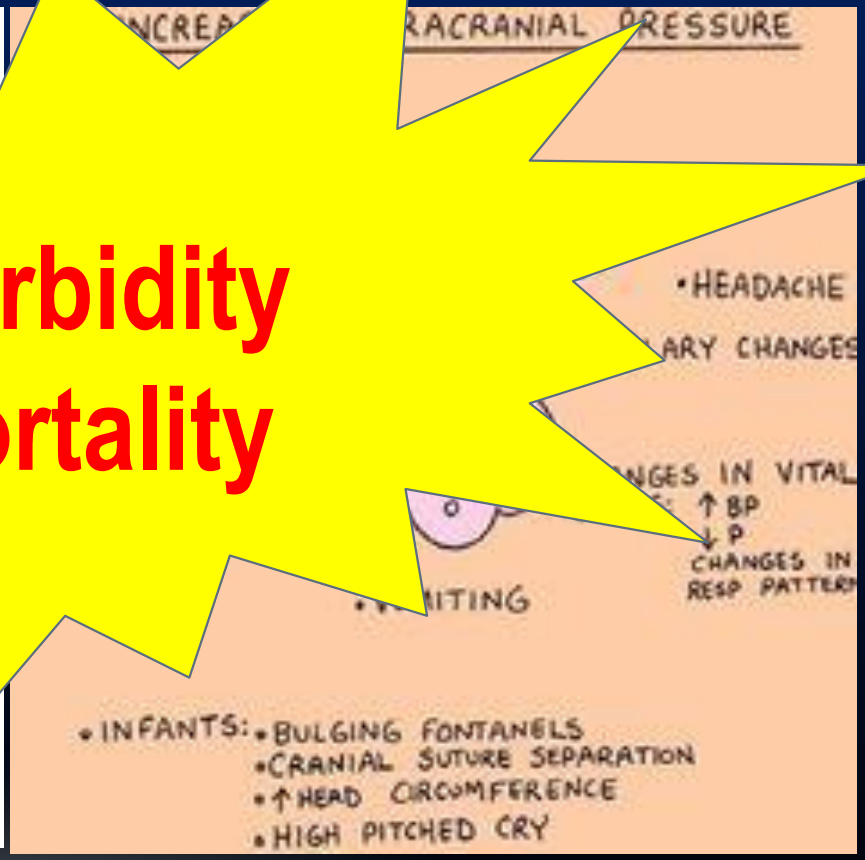


$$V_{blood} + V_{brain} + V_{CSF} = \text{Constant}$$

Austin Health

SYMPTOMS OF INCREASED ICP





Morbidity
Mortality

P.J. HUTCHINSON, P.J. KIRKPATRICK ; DECOMPRESSIVE CRANIECTOMY IN HEAD INJURY
CURRENT OPINION IN CRITICAL CARE 10:101-104, 2004

Herniation

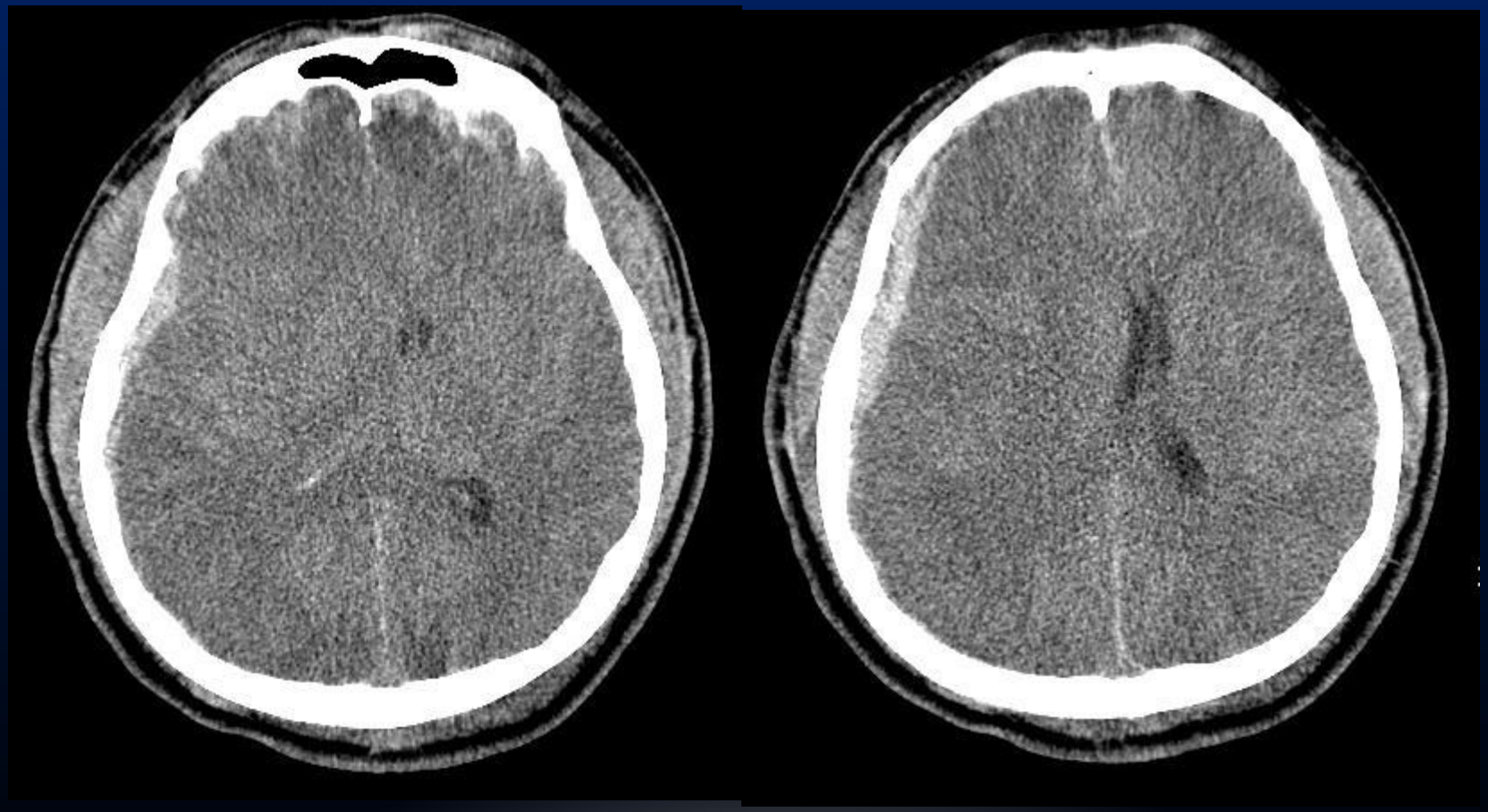
Increased ICP

Energy failure

Decrease O
delivery

crease CBF

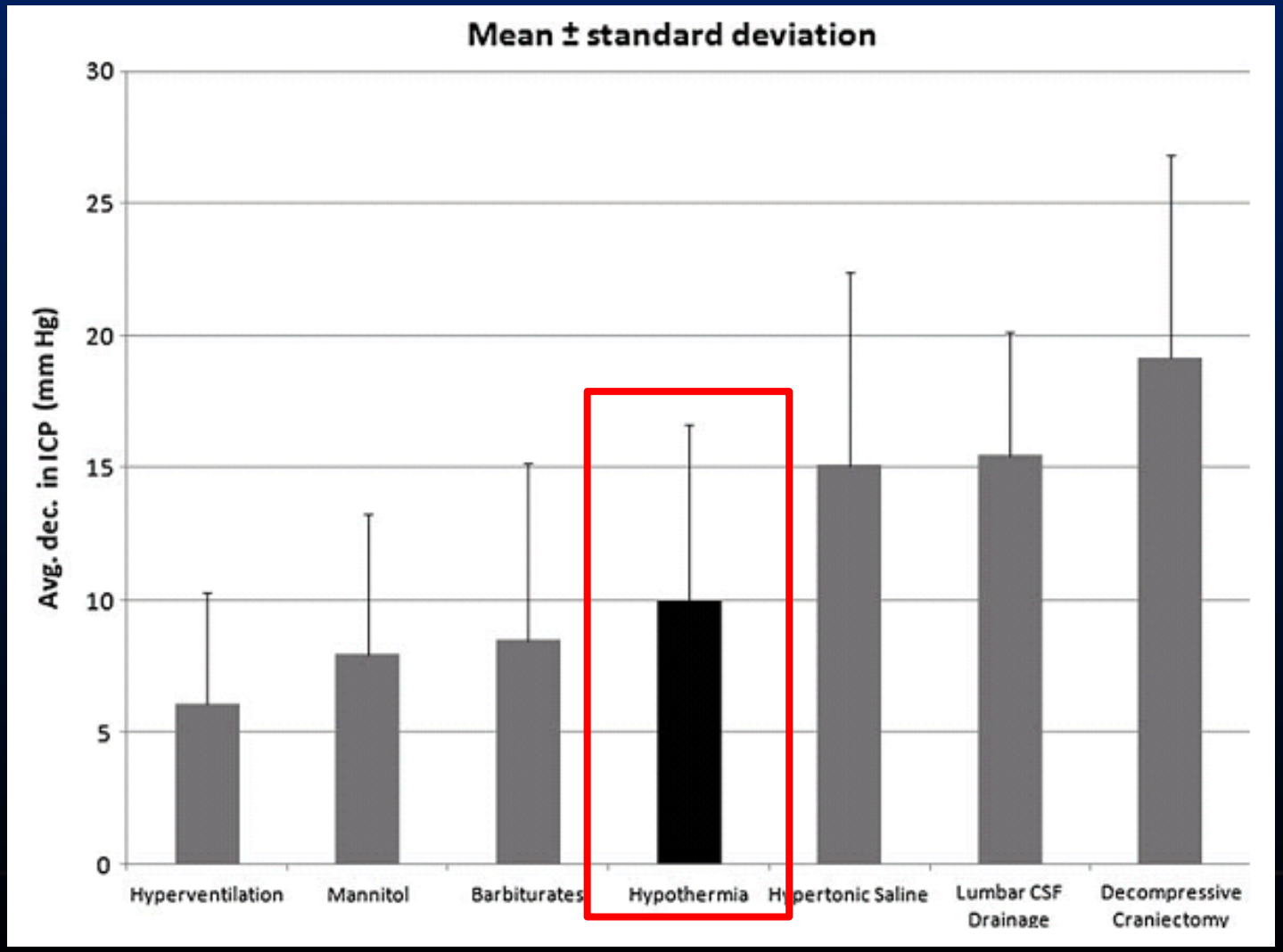
Escalating cycle of brain swelling



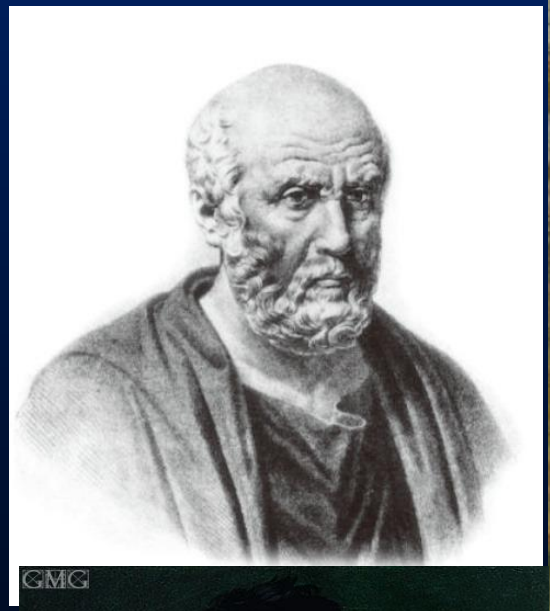
MANAGEMENT TO INCREASED ICP

- Head elevation 30 degrees
- Mannitol
- Hyperventilation
- Steroid
- Hypertonic solution
- CSF drainage
- Decompressive craniectomy
- **Hypothermia**

EFFECTIVE OF TH



HISTORICAL BACK GROUND OF THERAPEUTIC HYPOTHERMIA(TH)



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campaign in 1812 in an effort to preserve injured limbs as well as for its numbing effects during amputation.

HISTORICAL BACK GROUND OF THERAPEUTIC HYPOTHERMIA(TH)

- In 1937, Dr. Temple Fay “cooled” a patient to 32° C for 24 h, in an attempt to prevent cancer cells from further multiplying.
- Smith and Fay in 1940, reported the physiologic effects that induced TH caused in a series of cancer patients.
- In 1953, using canine and monkey models, Bigelow and McBirnie, published a study reporting the beneficial effect of TH for the brain and the heart during cardiac surgery.
- Rosomoff and Gilbert demonstrated a direct effect between body temperature, and intracranial pressure and brain volume in 1955. These early investigators confirmed that TH reduced the cerebral oxygen consumption, blood flow, and metabolic rate of a normal dog brain.
- By 1959, induced TH was widely used by neurosurgeons for head and spinal cord injuries as well as during cardiac surgery.

Effects of posttraumatic MgSO4 and hypothermia an animal model of TBI. Journal of Korean Neurological Society 29(10)1296-1302, 2000

Hyun DK et al

Using Marmarou model(1m height weight drop)
hypothermia 32°C, I hour , MgSO4 750μmol

hypothermia and MgSO4 significant improve pathological changes. In all treated group, a significant reduction in TUNEL positive cells and beta APP stainning were found in comparison with the control group each time(12hrs, 24hrs, 1wk and 2wks).
Hypothermia group is better neuroprotection on 2 wks

Otherwise simultaneously MgSO4 and hypothermia treatment group is failed to provide additional neuroprotection.

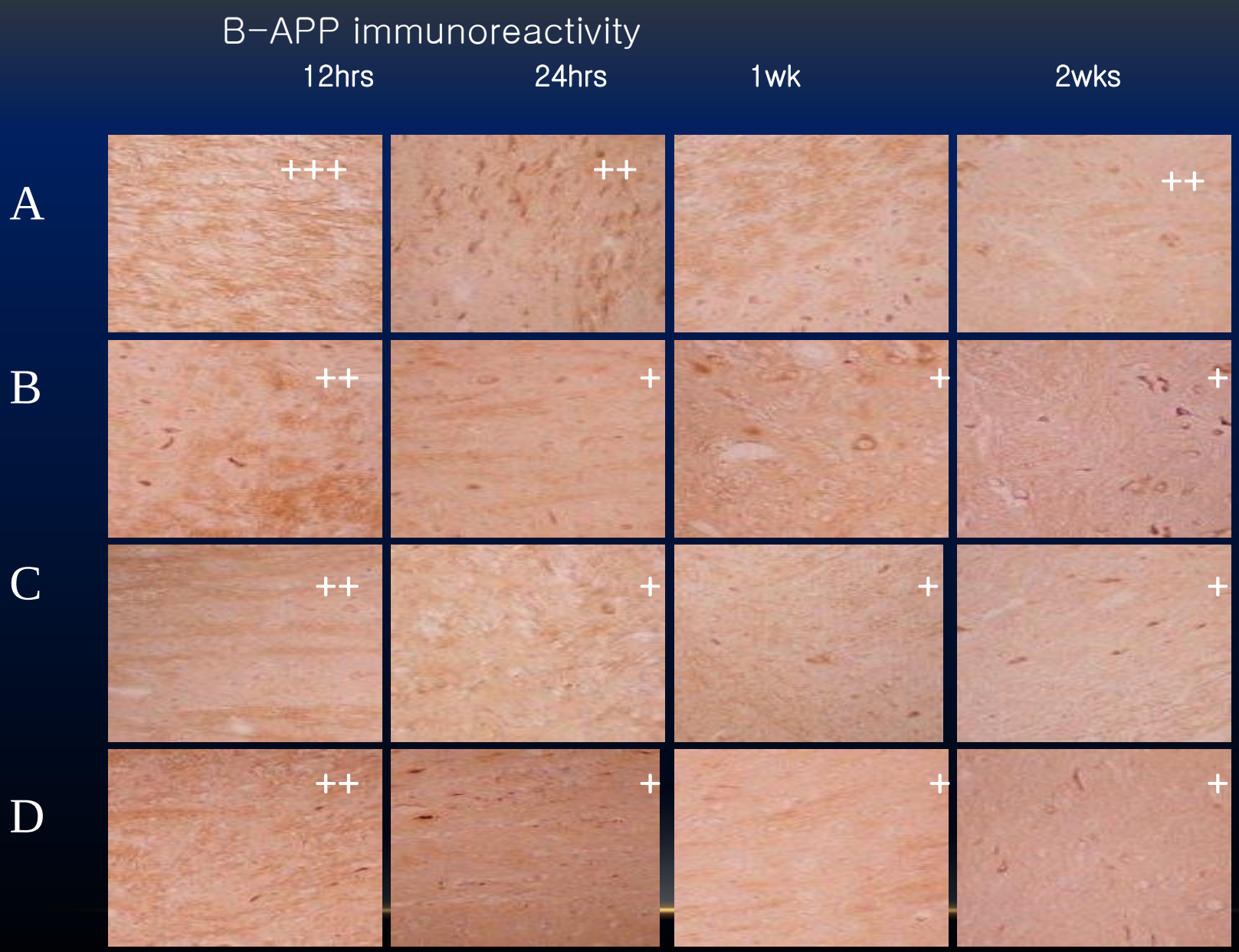


Fig4. Photographs of β-APP immunohistochemical staining.Groups treated with $MgSO_4$(B), or hypothermia(C), or $MgSO_4$ and hypothermia combined(D) show significant reduction of immunoreactivity (dark brown color and elongated or circular shape) compared with control group(A) at each times ($P<0.0001$). Original magnification(x100)

APOPTOSIS

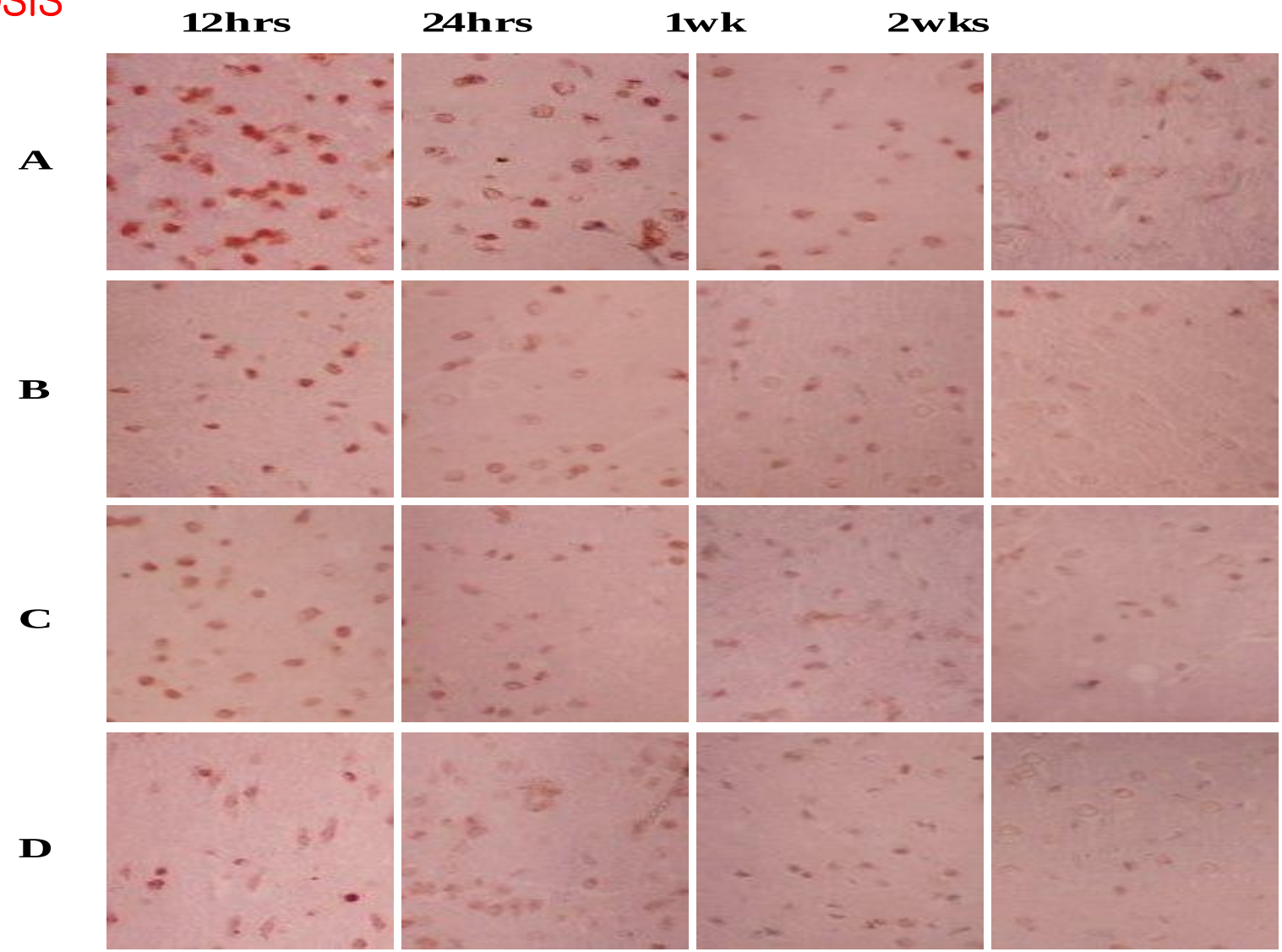


Fig5 Photographs of TUNEL staining (showing apoptosis). These show significant reduction of apoptosis (pinkish condensed cytoplasm, chromatin and membrane blebbing) in treatment groups - $MgSO_4$(B), hypothermia(C), $MgSO_4$ and hypothermia combined(D) - compared with control group(A) each times ($P<0.001$). As passing time, siginificant reduction is seen all groups ($P<0.001$). Original magnification (x100).

Apoptotic index of each group in TUNEL stain

	12 hours	24hours	1 week	2 weeks
control	50±0.7	38.6±4.0	29.8±0.6	17.6±1.7
MgSO4	35.6±2.6	24±3.4	20.6±2.2	11.4±0.2
Hypothermia	31±1.3	22.4±1.3	15±3.6	3.5±2.0
MgSO4 with Hypothermia	35.4±3.1	23±1.1	19.2±3.7	5.4±1.6

CURRENT UTILIZATION OF HYPOTHERMIA

- Cardiac arrest
- Traumatic brain injury / Ischemic stroke
- Perinatal asphyxia
- Cardiac surgery
- Neurosurgery
- Vascular surgery

MECHANISM OF TH

decreased

- Celluar energy requirements (6%/1˚C)
- Excitatory neurotransmitter release
- Oxygen free radical production
- Ischemic depolarizations in the penumbra
- Cytoskeletal proteolysis
- Neutrophil infiltration
- Cytokine and leukotriene production
- Apoptotic signaling (cell death)
- Epileptic activity and seizures

increased

- BBB stability
- Calcium-dependent intracellular signaling
- Protein synthesis and gene expression

Inducti
Max
sali
Use
prev
Sed

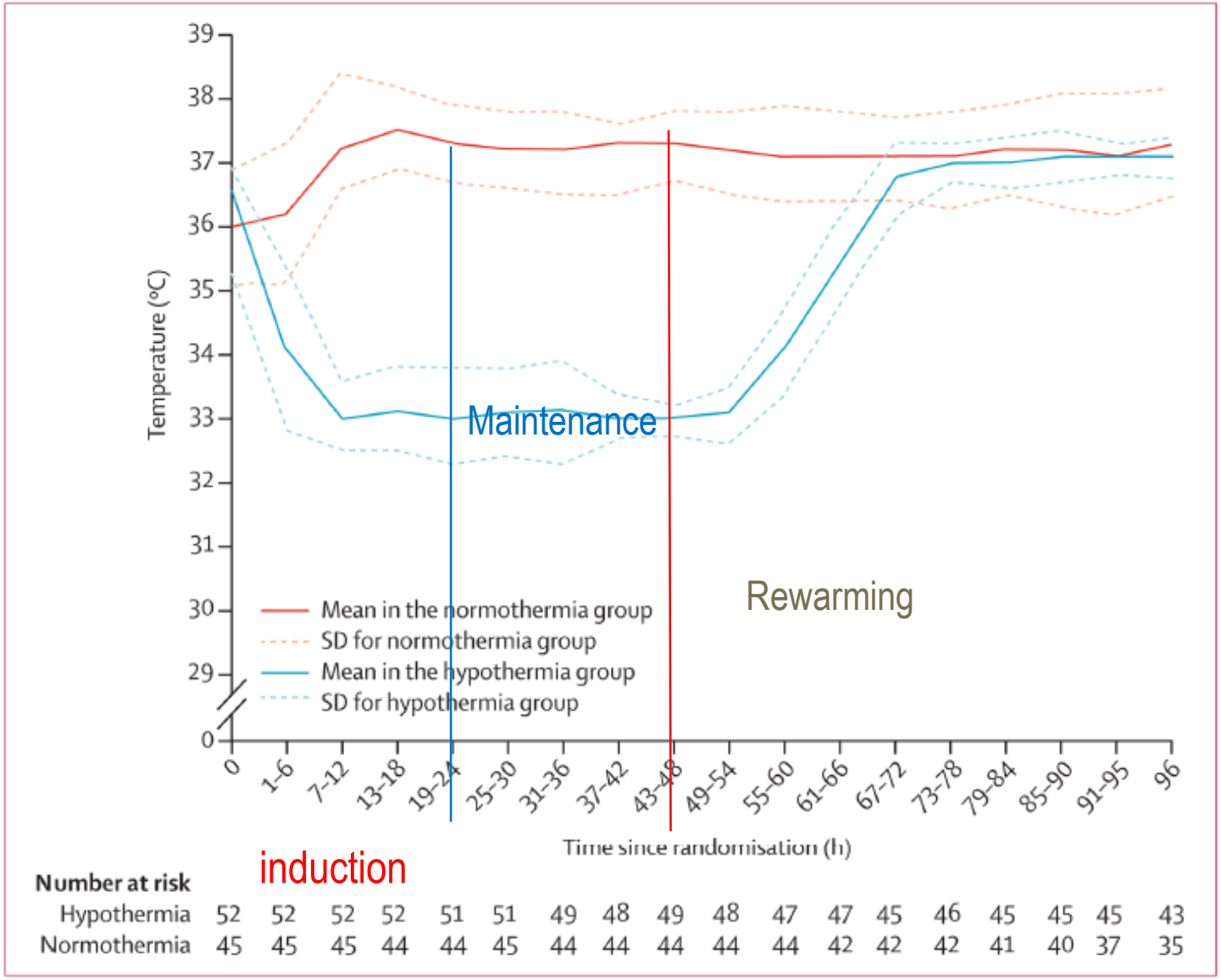


Figure 2. Temperature analysis during the first 96 h after randomisation
The number of patients decreased over time as patients died or were discharged from intensive care.

ain swelling,

tion &

paralytics

COMPLICATIONS OF TH

Changes on drug metabolism
Coagulopathy
Electrolytes shifts/disturbances
Ileus
Increased creatine/liver enzymes
Insulin resistance
Lactic acidosis
Pancreatitis
Pneumonia
Postcooling diuresis
Wound infection

CINCINNATI SUB – ZERO

Update of previous blanketrol II device

Covers more surface area

Bedside unit allows for more programmable options for depth/rate of cooling

Actual rates of cooling?

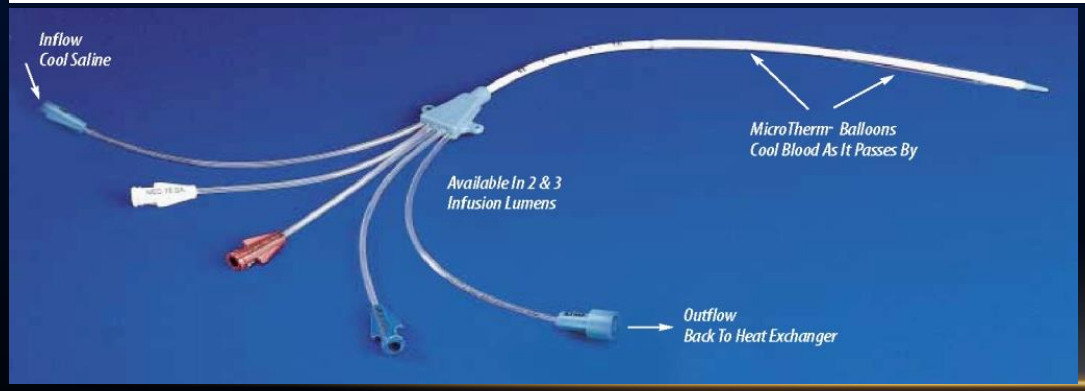
ALSIUS: COOLGARD SYSTEM

Triple lumen subclavian catheter (9.3 F)

Standard central catheter length (22 cm)

Three lumens for infusion

Two lumens to bedside unit for circulation of sterile saline through micro-balloons (closed-loop)



LIFE RECOVERY SYSTEMS: THERMOSUIT

- Extremely rapid cooling by ice water immersion
- Esophageal temperature probe
- Await more extensive clinical experience

CHOCHRANE

- Chochrane study : hypothermia of traumatic head injury
  - Multicenter, randomized controlled trials, 23 trials until 2009
  - 1614 pts. enrolled

- Study design
  - Multicenter, randomized
  - Any closed traumatic head injury requiring hospitalisation
  - Hypothermia (35˚C) at least 12 consecutive hours
  - Whole body cooling or just the head
  - Compare with normothermia group
  - Primary outcomes
    - Mortality & unfavorable outcome
  - Secondary outcomes
    - The frequency of pneumonia

[Intervention Review]

Hypothermia for traumatic head injury

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Editorial group: Cochrane Injuries Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2009.
Review content assessed as up-to-date: 6 April 2009.

Citation: Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD001048. DOI: 10.1002/14651858.CD001048.pub4.

ABSTRACT

Background

Hypothermia has been used in the treatment of head injury for many years. Encouraging results from small trials and laboratory studies led to renewed interest in the area and some larger trials.

Objectives

To estimate the effect of mild hypothermia for traumatic head injury on mortality and long-term functional outcome complications.

Search methods

We searched the Cochrane Injuries Group Specialised Register, Current Controlled Trials *Meta*Register of trials, Zetoc, ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index-Science (CPCI-S), CENTRAL (*The Cochrane Library*), MEDLINE and EMBASE. We handsearched conference proceedings and checked reference lists of all relevant articles. The search was last updated in April 2009.

Selection criteria

Randomised controlled trials of hypothermia to a maximum of 35°C for at least 12 consecutive hours versus control in patients with any closed traumatic head injury requiring hospitalisation. Two authors independently assessed all trials.

Data collection and analysis

Data on death, Glasgow Outcome Scale and pneumonia were sought and extracted, either from published material or by contacting the investigators. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each trial on an intention-to-treat basis.

Main results

We found 23 trials with a total of 1614 randomised patients. Twenty-one trials involving 1587 patients reported data on deaths. There were fewer deaths in patients treated with hypothermia than in the control group (OR 0.85, 95% CI 0.68 to 1.06). Nine trials with good allocation concealment showed no decrease in the likelihood of death with hypothermia compared with the control group (OR 1.11, 95% CI 0.82 to 1.51). In both cases the result was not statistically significant. Twenty-one trials involving 1587 patients reported data on unfavourable outcomes (death, vegetative state or severe disability). Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.77, 95% CI 0.62 to 0.94). Nine trials with good allocation concealment showed patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group, but the reduction was small and non-significant (OR 0.93, 95% CI 0.70 to 1.23). Hypothermia treatment was associated with a slight increase in the odds of pneumonia (OR 1.35, 95% CI 0.95 to 1.91) but there was a reduction in pneumonia for trials with good allocation concealment (four trials analysed separately, 306 patients, OR 0.84, 95% CI 0.52 to 1.35) although in both cases the results are not statistically significant.

Authors' conclusions

There is no evidence that hypothermia is beneficial in the treatment of head injury. Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. Low quality trials have a tendency to overestimate the treatment effect. The high quality trials found no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant and could be due to the play of chance. Hypothermia should not be used except in the context of a high quality randomised controlled trial with good allocation concealment.

PLAIN LANGUAGE SUMMARY

Hypothermia (body temperature cooling) for traumatic head injury

This review includes twenty-three randomised controlled trials involving 1614 patients with traumatic head injury. In each trial, the patients were randomly divided into two groups: one group remained at normal body temperature, and the other group was cooled to a maximum of 35 degrees Celsius (or 95 degrees Fahrenheit) for at least 12 consecutive hours. Cooling could be of the whole body (e.g. with a blanket with circulating cold water), or just the head (e.g. with a helmet with circulating cold water). Information on death, disability, and pneumonia were evaluated for each trial.

The review authors found that fewer people died or became severely disabled if they were treated with hypothermia, but this finding may be due to chance. It was also found that patients given hypothermia were more likely to develop pneumonia, and some patients died from pneumonia, but the increased risk of pneumonia could also be due to chance.

Some of the trials included in the review were of low methodological quality. Low quality trials have a tendency to overestimate the effect of a treatment. In this review, the lower quality trials showed hypothermia treatment to be somewhat effective in reducing death and disability among patients with head injury. However, the good quality trials showed no decrease in the likelihood of death with hypothermia treatment and a reduced likelihood of pneumonia. Some of the findings in this review are therefore contradictory, and this is probably due to the inclusion of data from low quality trials.

The review authors conclude that there is no evidence that hypothermia is beneficial in the treatment of head injury. Most of the positive and negative effects found may be due to chance. Hypothermia should not be used except in the context of a randomised controlled trial with good allocation concealment.

There is no evidence that hypothermia is beneficial in the treatment of head injury

BACKGROUND HYPOTHERMIA AFTER TBI

- Houston group, Clifton, 1993
  - Phase II study
  - 33° C within 8 hrs, maintain for 48 hrs
  - Good outcome (good recovery, mod disabiligy in GOS): 15% improvement
- Pittsburg group, Marion, 1997
  - Phase II study
  - 33° C within 10 hrs, maintain for 24 hrs
  - Good outcome: 24% improvement
- No significant hypothermia-related toxicity

NABIS:H (National Acute Brian Injury Study: Hypothermia) by NINDS, 1994

NIND(National Institute of Neurological Disorders and Stroke).

NABIS:H

- Randomized, prospective, multicenter trial, 500 pt
- Surface cooling induced moderate hypothermia (33° C) within 6 hrs of severe TBI (GCS≤8), maintain for 48 hrs
- Functional outcome: GOS at 6 mos
- Stop in May 1998 after enrolling 392 pt
  - The Patient Safety and Monitoring Board
  - Low probability of detecting a treatment effect (Class I)
- No difference in outcome between hypothermia & normothermia
- Hypothermia blunt major elevations of ICP

NEJM 2001; 344: 556-64

CLINICAL EVIDENCE OF HYPOTHERMIA

NABIS:H

- Result
  - Poor in both groups
    - Severe disability, vegetative, death
  - Mortality
    - hypothermia vs normothermia 28% VS 27% ($p=0.79$)
  - More hospital days and complication in hypothermia group

- Conclusion: No effect of hypothermia

NABIS:H

Tx group		Pt with admission temp ≤ 35°C			Pt with admission temp > 35°C		
		No.	% Poor outcome	*p* Value	No.	% Poor outcome	*p* Value
All Pt		102		0.09	264		0.7
	hypothermia	62	61		127	54	
	normothermia	40	78		137	52	
Pt≤45 yrs		81		0.02	233		0.84
	hypothermia	48	52		115	51	
	normothermia	33	76		118	50	
Pt>45 yrs		21		0.60	31		0.23
	hypothermia	14	93		12	83	
	normothermia	7	86		19	63	

Outcome at 6 mos, poor outcome: severe disability, vegetative state or death in GOS

CAUSE OF HYPOTHERMIA ON ADMISSION

NABIS:H

- Hypothermia on admission
  - < 35° C
  - Envirionmental (Class II or III)
    - Winter month
    - Receipt of larger volumes of room-temp IV fluids
    - Positive blood alcohol level
    - Smaller body size
    - Increased age
    - Prehospital hypotension
  - Detrimental to rewarm hypothermic pt on admission

HYPOTHERMIC EFFECT ON ICP

NABIS:H

- Treatment effect of hypothermia on IICP (Class I & II)
  - NABIS:H
    - All pt group: reduce incidence of ICP>30 mmHg
    - Over 45 yrs, normothermic on admission: no effect
  - Hypothermia to control IICP improve outcome (Class I & II)

Selective use of hypothermia to treat established IICP treat the early biochemical cascade occurring immediately after injury

RECOMMENDATIONS

NABIS:H

- Not possible to recommend (Level I)
  - Use of hypothermia as a treatment for severe TBI
- Options
  - Possible that very early induction of hypothermia may improve outcome
    - Hypothermic (≤ 35%) pt on admission
    - ≤ 45 yrs of age
  - Hypothermia may reduce marked IICP (>30 mmHg) in selective pt

CRITIQUES

NABIS:H

- Marked inter-center variance
  - Treatment effect of hypothermia
  - Age of participants
  - Severity of illness scoring between groups
  - Management of IICP
  - Hemodynamic and fluid management
- More favorable outcome at large patient volume centers
  - Different treatment quality between centers

META-ANALYSIS FOR TBI

- BTF/AANS, 1996 to 2002
  - 8 trials, 781 patients
  - With more than 48 hr hypothermia
    - Reduction in risk of mortality *RR 0.51*
    - Favorable neurologic outcome *RR 1.91*
    - Risk of pneumonia *RR 2.37*
- National Guideline 2007

  Recommendation for optional & cautious use of hypothermia for adult TBI (*Level III*)

Peterson, J Neurotrauma 2008 25:62-71

NABIS: H II

Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial

Guy L Clifton, Alex Valadka, David Zygun, Christopher S Coffey, Pamala Drever, Sierra Fourwinds, L Scott Janis, Elizabeth Wilde, Pauline Taylor, Kathy Harshman, Adam Conley, Ava Puccio, Harvey S Levin, Stephen R McCauley, Richard D Bucholz, Kenneth R Smith, John H Schmidt, James N Scott, Howard Yonas, David O Okonkwo

Lancet Neurol 2011 10:131-139

- RCT in US and Canada
  - 16-45 years old
  - Severe TBI (GCS≤8)
  - Hypothermia within 2.5 hr
    - 35℃ using iv 2L of cold crystalloid, wet sheets, gel packs
    - 33℃ using Arctic Sun (Medivance®), ventillated air, chilled cristalloid, gastric lavage with cold water
  - Maintain for 48 hr
  - Rewarming: 0.5℃ every 2 hr

- Functional outcome: GOS at 6mos
- Stop in June 2009 after enrolling 232 patients
- No difference in outcome between hypothermia & normothermia
- Surgical removal of ICH: fewer poor outcome in hypothermia

NABIS: H II

	Poor outcome			Died		
	n (%)	RR (95% CI)	p value	n (%)	RR (95% CI)	p value
Primary analysis						
All patients (n=97)	56 (58%)	..	..	20 (21%)	..	..
Hypothermia (n=52)	31 (60%)	1·08 (0·76–1·53)	0·67	12 (23%)	1·30 (0·58–2·89)	0·52
Normothermia (n=45)	25 (56%)	..	..	8 (18%)	..	..
Subgroup analysis						
Diffuse brain injury (n=69)	42 (61%)	..	..	13 (19%)	..	..
Hypothermia (n=37)	26 (70%)	1·44 (0·95–2·17)	0·09	10 (27%)	2·88 (0·87–9·57)	0·08
Normothermia (n=32)	16 (50%)	..	..	3 (9%)	..	..
Surgically removed haematomas (n=28)	14 (50%)	..	..	7 (25%)	..	..
Hypothermia (n=15)	5 (33%)	0·44 (0·22–0·88)	0·02	2 (13%)	0·35 (0·08–1·50)	0·16
Normothermia (n=13)	9 (69%)	..	..	5 (39%)	..	..

Data are number (%). RR=relative risk.

Table 2: Outcome and mortality rates

PROBLEMS IN TRIALS

- Standardization of selection criteria
- Method of cooling
- Depth and duration of cooling
- Strategies for rewarming
- Treatment of complication
- Difference in outcome measure
- F/U period

EUROTHERM 3235 TRIAL

STUDY PROTOCOL Open Access

European society of intensive care medicine study of therapeutic hypothermia (32-35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial)

Peter JD Andrews[1*], Helen Louise Sinclair[1], Claire G Battison[1], Kees H Polderman[2], Giuseppe Citerio[3], Luciana Mascia[4], Bridget A Harris[1], Gordon D Murray[5], Nino Stocchetti[6], David K Menon[7], Haleema Shakur[8], Daniel De Backer[9], the Eurotherm3235Trial collaborators

Abstract

Background: Traumatic brain injury is a major cause of death and severe disability worldwide with 1,000,000 hospital admissions per annum throughout the European Union.
Therapeutic hypothermia to reduce intracranial hypertension may improve patient outcome but key issues are length of hypothermia treatment and speed of re-warming. A recent meta-analysis showed improved outcome when hypothermia was continued for between 48 hours and 5 days and patients were re-warmed slowly (1°C/4 hours). Previous experience with cooling also appears to be important if complications, which may outweigh the benefits of hypothermia, are to be avoided.

Methods/design: This is a pragmatic, multi-centre randomised controlled trial examining the effects of hypothermia 32-35°C, titrated to reduce intracranial pressure <20 mmHg, on morbidity and mortality 6 months after traumatic brain injury. The study aims to recruit 1800 patients over 41 months. Enrolment started in April 2010.
Participants are randomised to either standard care or standard care with titrated therapeutic hypothermia. Hypothermia is initiated with 20-30 ml/kg of intravenous, refrigerated 0.9% saline and maintained using each centre's usual cooling technique. There is a guideline for detection and treatment of shivering in the intervention group. Hypothermia is maintained for at least 48 hours in the treatment group and continued for as long as is necessary to maintain intracranial pressure <20 mmHg. Intracranial hypertension is defined as an intracranial pressure >20 mmHg in accordance with the Brain Trauma Foundation Guidelines, 2007.

Discussion: The Eurotherm3235Trial is the most important clinical trial in critical care ever conceived by European intensive care medicine, because it was launched and funded by the European Society of Intensive Care Medicine and will be the largest non-commercial randomised controlled trial due to the substantial number of centres required to deliver the target number of patients. It represents a new and fundamental step for intensive care medicine in Europe. Recruitment will continue until January 2013 and interested clinicians from intensive care units worldwide can still join this important collaboration by contacting the Trial Coordinating Team via the trial website http://www.eurotherm3235trial.eu.

Trial registration: Current Controlled Trials ISRCTN34555414

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 17, 2015 VOL. 373 NO. 25

- Pragmatic multi-center randomised controlled trial
- Effect of TH 32~35˚C

→ reduce ICP<20mmHg on morbidity and mortality 6 month after TBI

- 387 patients at 47 centers in 18 countries (2009.11 ~2014.10)
- The adjusted common odds ratio for the GOS-E score was 1.53 (95% confidence interval, 1.02 to 2.30; P = 0.04), indicating **"A worse outcome in the hypothermia group than in the control group."**

EUROTHERM 3235 TRIAL

- Methods/design

Inclusion Criteria	*Exclusion Criteria*
1) Believed to be legal age for consent to take part in research to 65 years of age 2) Primary closed TBI 3) Raised ICP >20 mmHg for ≥5 minutes after first line treatments with no obvious reversible cause e.g. patient position, coughing, inadequate sedation 4) ≤72 hours from the initial head injury 5) Cooling device or technique available for >48 hours 6) Core temperature ≥36°C (at the time of randomisation) 7) An abnormal CT scan of the brain. This is defined as one that shows haematoma, contusion, swelling, herniation or compressed basal cisterns.	1) Patient already receiving therapeutic hypothermia treatment 2) Administration of barbiturate infusion prior to randomisation 3) Unlikely to survive for the next 24 hours in the opinion of the ICU Consultant or Consultant Neuro-surgeon treating the patient 4) Temperature ≤34°C at hospital admission 5) Pregnancy (all female patients of child bearing age who meet the inclusion criteria will undergo a urine pregnancy test. This is performed as part of the screening for eligibility procedure by the investigator or research nurse in the ICU).

EUROTHERM 3235 TRIAL

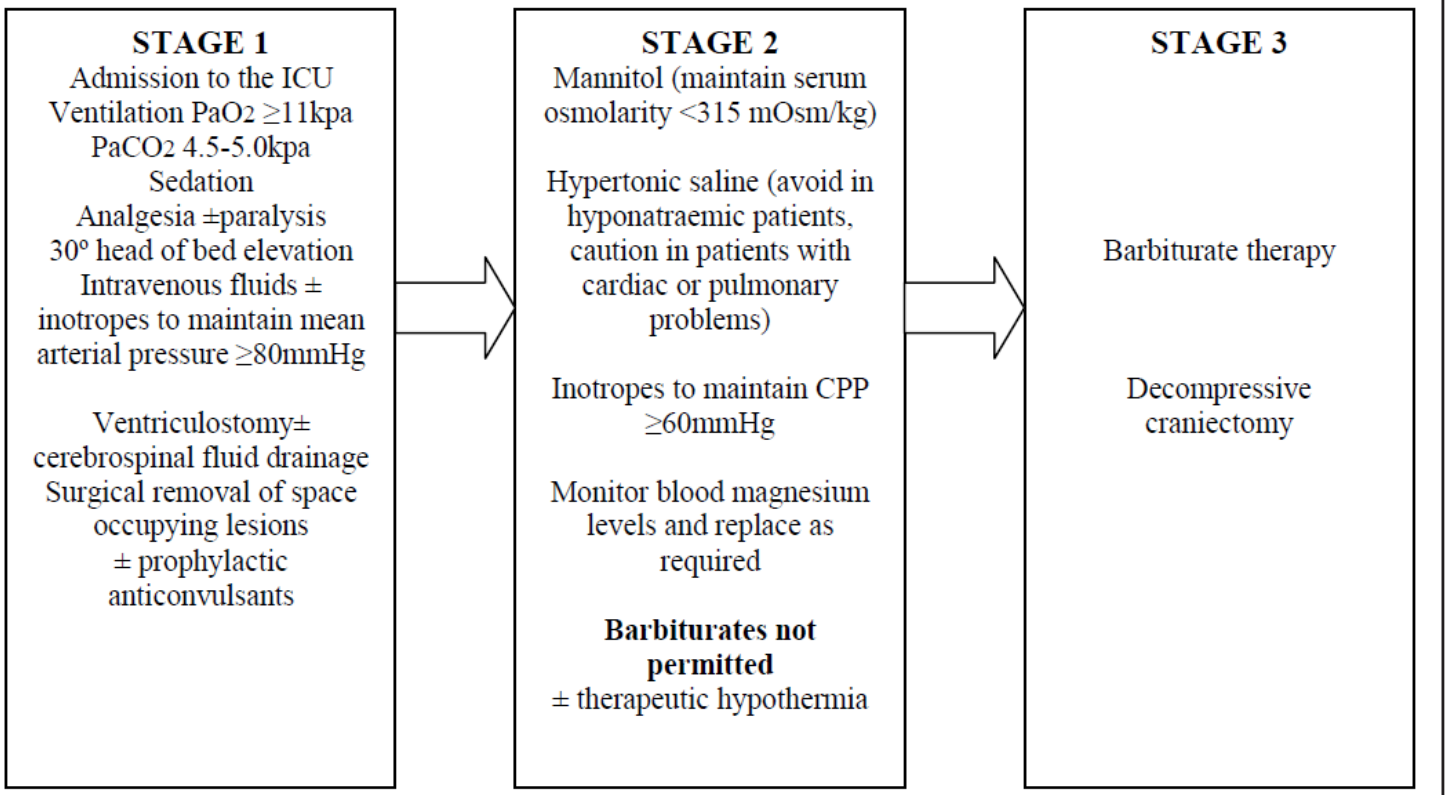
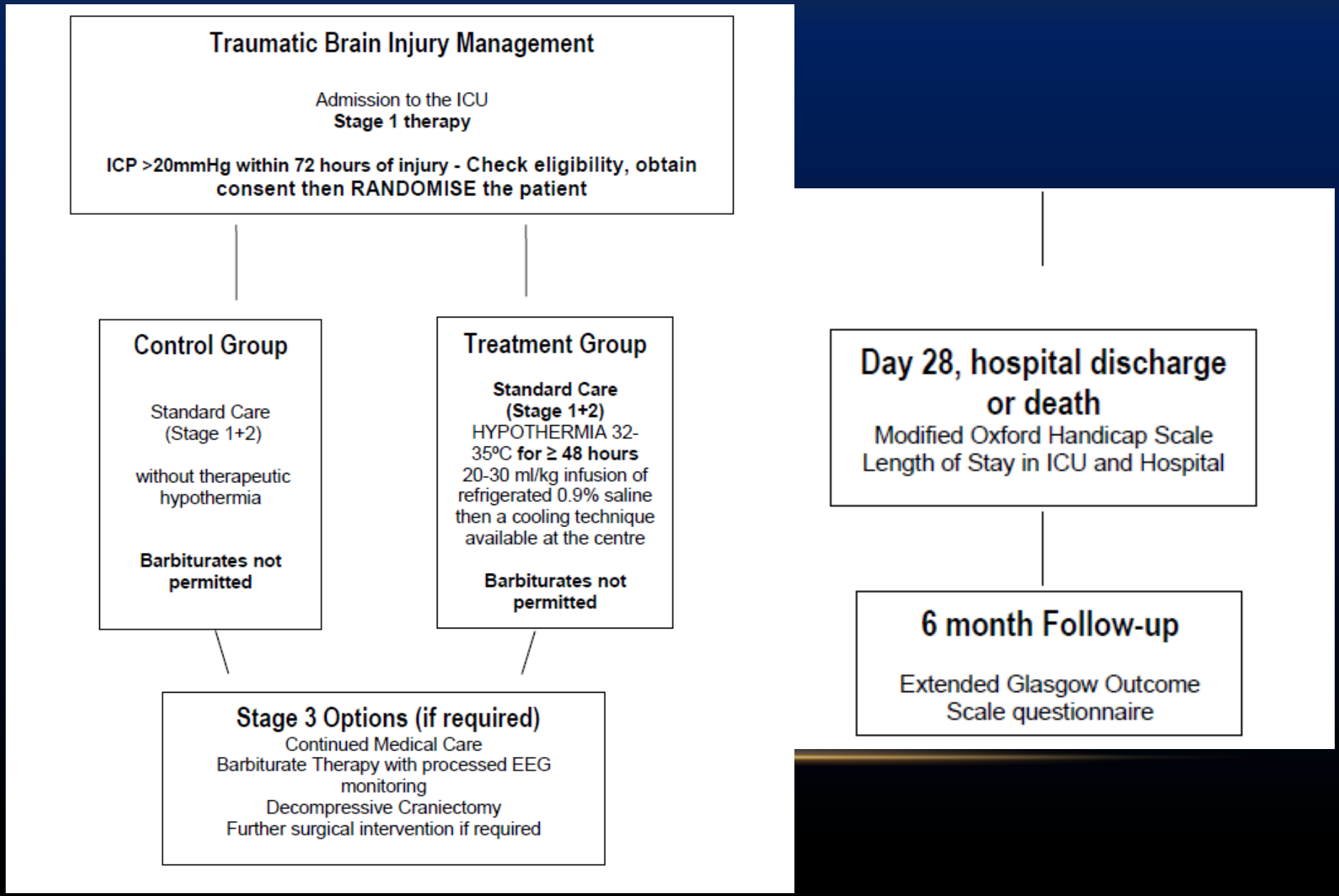


Figure 1 Stages of therapeutic management of raised intracranial pressure after traumatic brain injury [37,43].

EUROTHERM 3235 TRIAL



JAPAN NEUROTRAUMA DATA BANK

JOURNAL OF NEUROTRAUMA 31:315–320 (February 15, 2014)

DOI: 10.1089/neu.2013.3057

Original Articles

Survey of Brain Temperature Management in Patients with Traumatic Brain Injury in the Japan Neurotrauma Data Bank

Eiichi Suehiro,[1,2] Hiroyasu Koizumi,[1,2] Ichiro Kunitsugu,[3] Hirosuke Fujisawa,[1,2] and Michiyasu Suzuki[1,2]

Abstract

The goal of this study was to evaluate the clinical characteristics and effects of brain temperature management in patients with severe traumatic brain injury (TBI). A total of 1091 patients were registered from the Japan Neurotrauma Data Bank Project 2009. Those with a Glasgow Coma Scale (GCS) score of 9 or more, a GCS score of 3, bilateral dilated pupils, or cardiopulmonary arrest on arrival were excluded. This left a total of 401 patients. Patients were classified into three groups: no temperature management, with no intervention for brain temperature (225 patients, 56.1%), intensive normothermia (129 patients, 32.2%), and hypothermia (47 patients, 11.7%). Patient age, GCS score, pupillary abnormality, Injury Severity Score (ISS), intracranial pressure (ICP) monitoring, and outcome according to CT classification (Traumatic Coma Data Bank classification) on admission were examined. Patients were significantly older in the no temperature management group (average age 61.5 years) compared with normothermia (53.6 years) and hypothermia (46.9 years). ICP monitoring was significantly decreased in 85.1% of patients with hypothermia, 42.6% with normothermia, and 14.7% in no temperature management group. Favorable outcome rate was significantly higher with hypothermia (52.4%) compared with normothermia (26.9%) and no temperature management (20.7%) with evacuated mass lesions in contrast to diffuse injury. Multivariate analysis in patients with evacuated mass lesions showed that GCS (≥ 6 pts), and hypothermia were independent factors related to a favorable outcome. Appropriate thermoregulation of the brain for individual patients with various types of TBI are important.

Key words: brain temperature management; CT classification (TCDB classification); severe traumatic brain injury; survey

JAPAN NEUROTRAUMA DATA BANK

Study design

- 1091 pts Japan neurotrauma databank
- GCS 4~8 enrolled
- Total 401 pts classified 3 group
  - No temp manage 225pts, 56.1%

    (average age 61.5 yrs)
  - Intensive normothermia 129 pts, 32.2% (average age 53.6 yrs)
  - Hypothermia 47 pts, 11.7%

    (average age 46.9 yrs)

on admission examined.

- Patient age,
- GCS score,
- pupillary abnormality,
- Injury Severity Score (ISS),
- intracranial pressure (ICP) monitoring
- outcome according to CT classification

JAPAN NEUROTRAUMA DATA BANK

- "no temperature management" group did not receive brain temperature management, but received routine medical management including ice packs or drugs to control high fever.

- Brain temperature was maintained strictly below 38C with cooling blankets in patients with "normothermia."

- Patients in the "hypothermia" group received temperature treatments, with temperatures maintained below 35C.

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TABLE 1. SUMMARY OF RESULTS IN ALL PATIENTS

	No temperature management (C)	*Normothermia (N)*	*Hypothermia (H)*	p *value*
No. of cases (%)	225 (56.1)	129 (32.2)	47 (11.7)	
Male (%)	157 (69.8)	88 (68.2)	36 (76.6)	NS
Age (years)	61.5 ± 24.0	53.6 ± 22.6	46.9 ± 24.6	0.01 C vs. N, 0.0007 C vs. H
GCS score	6.2 ± 1.4	6.2 ± 1.3	6.3 ± 1.4	NS
Pupil abnormality (%)	68 (30.2)	48 (37.2)	15 (31.9)	NS
ISS	25.6 ± 11.4	26.3 ± 10.9	26.0 ± 8.6	NS
ICP monitoring (%)	33 (14.7)	55 (42.6)	40 (85.1)	< 0.0001 C vs. N, < 0.0001 C vs. H, < 0.0001 N vs. H
Favorable outcome (%)	57 (25.3)	43 (33.3)	21 (44.7)	0.0076 C vs. H
Mortality (%)	69 (30.7)	31 (24.0)	16 (34.0)	NS

NS, not significant; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; ICP, intracranial pressure.

TABLE 2. SUMMARY OF RESULTS IN PATIENTS WITH DIFFUSE INJURY I ~ IV

Parameters	*Total*	*No temperature management (C)*	*Normothermia (N)*	*Hypothermia (H)*	p *value*
No. of cases (%)	158	88 (55.7)	49 (31.0)	21 (13.3)	
Male (%)	117 (74.1)	67 (76.1)	36 (73.5)	14 (66.7)	NS
Age (years)	49.2 ± 23.8	54.2 ± 23.2	43.8 ± 23.1	41.0 ± 24.3	0.0456 C vs. N
GCS score	6.3 ± 1.3	6.4 ± 1.3	6.2 ± 1.3	6.0 ± 1.4	NS
Pupil abnormality (%)	33 (20.9)	14 (15.9)	12 (24.5)	7 (33.3)	NS
ISS	26.9 ± 12.5	27.1 ± 12.8	27.6 ± 13.4	24.6 ± 8.5	NS
ICP monitoring (%)	44 (27.8)	8 (9.1)	18 (36.7)	18 (85.7)	<0.0001 C vs. N, <0.0001 C vs. H <0.0002 N vs. H
Favorable outcome (%)	56 (35.4)	29 (33.0)	19 (38.8)	8 (38.1)	NS
Mortality (%)	42 (26.6)	21 (23.9)	12 (24.5)	9 (42.9)	NS

NS, not significant; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; ICP, intracranial pressure.

→ No significant favorable outcome among 3 group

JAPAN NEUROTRAUMA DATA BANK

TABLE 3. SUMMARY OF RESULTS IN PATIENTS WITH EVACUATED MASS LESION

Parameters	*Total*	*No temperature management (C)*	*Normothermia (N)*	*Hypothermia (H)*	p *value*
No. of cases (%)	160	87 (54.4)	52 (32.5)	21 (13.1)	
Male (%)	106 (66.3)	56 (64.4)	33 (63.5)	17 (81.0)	NS
Age (years)	60.7 ± 24.2	64.9 ± 25.7	57.8 ± 19.0	50.6 ± 26.3	NS
GCS score	6.0 ± 1.3	6.0 ± 1.4	6.0 ± 1.3	6.3 ± 1.4	NS
Pupil abnormality (%)	72 (45.0)	36 (41.4)	29 (55.8)	7 (33.3)	NS
ISS	25.1 ± 8.0	24.1 ± 7.9	25.8 ± 7.2	27.2 ± 9.6	NS
ICP monitoring (%)	67 (41.9)	19 (21.8)	29 (55.8)	19 (90.5)	< 0.001 C vs. N, < 0.001 C vs. H, 0.006 N vs. H
Favorable outcome (%)	43 (26.9)	18 (20.7)	14 (26.9)	11 (52.4)	0.003 C vs. H, 0.04 N vs. H
Mortality (%)	40 (25.0)	24 (27.6)	12 (23.1)	4 (19.0)	NS

NS, not significant; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; ICP, intracranial pressure.

→ Favorable outcome in hypothermia group

TABLE 4. SUMMARY OF RESULTS IN PATIENTS WITH NONEVACUATED MASS LESION

Parameters	*Total*	*No temperature management (C)*	*Normothermia (N)*	*Hypothermia (H)*	p *value*
No. of cases (%)	83	50 (60.2)	28 (33.7)	5 (6.0)	
Male (%)	59 (71.1)	35 (70.0)	19 (67.9)	5 (100)	NS
Age (years)	65.8 ± 19.8	68.4 ± 18.7	62.9 ± 22.0	55.6 ± 14.4	NS
GCS score	6.3 ± 1.4	6.1 ± 1.5	6.6 ± 1.2	6.8 ± 1.6	NS
Pupil abnormality (%)	26 (31.3)	18 (36.0)	7 (25.0)	1 (20.0)	NS
ISS	25.5 ± 12.6	25.7 ± 13.7	24.9 ± 11.8	27.4 ± 1.9	NS
ICP monitoring (%)	17 (20.5)	6 (12.0)	8 (28.6)	3 (60.0)	0.006 C vs H,
Favorable outcome (%)	22 (26.5)	10 (20.0)	10 (35.7)	2 (40.0)	NS
Mortality (%)	34 (41.0)	24 (48.0)	7 (25.0)	3 (60.0)	0.047 C vs N

NS, not significant; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; ICP, intracranial pressure.

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Results

Favorable outcome rate

hypothermia (52.4%)

normothermia (26.9%)

no temperature management (20.7%)

with evacuated mass lesions in contrast to diffuse injury.

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Conclusion

- patient outcomes with diffuse injury were not improved by hypothermia induction
- but hypothermia therapy was significant in protecting the brain of patients with evacuated mass lesions.

ONLY POSITIVE RESULT

% of poor outcome	n	Hypothermia	Normothermia	P-value
NABIS-H1 (>35˚C) at admission	73	55%	47%	0.70
NABIS-H1 (<35˚C) at admission	36	50%	94%	0.005
NABIS-H2 (Hematoma)	28	33%	69%	0.02

Japan Neurotrauma Data Bank. 2014

hypothermia (52.4%)
normothermia (26.9%)
no temperature management (20.7%)
with evacuated mass lesions in contrast to diffuse injury

B-HYPO 2015

Prolonged Mild Therapeutic Hypothermia versus Fever Control with Tight Hemodynamic Monitoring and Slow Rewarming in Patients with Severe Traumatic Brain Injury: A Randomized Controlled Trial

Tsuyoshi Maekawa,[1,2,*] Susumu Yamashita,[2,*] Seigo Nagao,[3] Nariyuki Hayashi,[4] and Yasuo Ohashi[5] on behalf of the Brain-Hypothermia (B-HYPO) Study Group[†]

PROLONGED MILD THERAPEUTIC HYPOTHERMIA VERSUS FEVER CONTROL WITH TIGHT HEMODYNAMIC MONITORING AND SLOW REWARMING IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY: A RANDOMIZED CONTROLLED TRIAL

JOURNAL OF NEUROTRAUMA 32:422–429 (APRIL 1, 2015)

- To determine the effect of therapeutic hypothermia, while **Avoiding some limitations of earlier studies**, which included
  - **patient selection based on Glasgow coma scale (GCS), delayed initiation of cooling, short duration of cooling, inter-center variation in patient care, and relatively rapid rewarming.**
- Methods:
  - Therapeutic hypothermia (**32–34 ℃**, n = 98) or fever control (35.5–37 ℃, n = 50),
  - for more than **72 hrs**, **rewarmed at a rate of < 1℃/day**
- **The primary outcome**: GOS at 6 months
- **Conclusions:** Tight hemodynamic management and slow rewarming, together with prolonged therapeutic hypothermia (32–34 ℃) for severe TBI, **"Did not Improve the neurological outcomes or risk of mortality"** compared with strict temperature control (35.5–37 ℃).

EFFECT OF EARLY SUSTAINED PROPHYLACTIC HYPOTHERMIA ON NEUROLOGIC OUTCOMES AMONG PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY: THE POLAR RANDOMIZED CLINICAL TRIAL.

JAMA. 2018 DEC 4;320(21):2211-2220

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients With Severe Traumatic Brain Injury
The POLAR Randomized Clinical Trial

D. James Cooper, MD; Alistair D. Nichol, MB, PhD; Michael Bailey, PhD; Stephen Bernard, MBBS, MD; Peter A. Cameron, MD; Sébastien Pili-Floury, MD, PhD; Andrew Forbes, PhD; Dashiell Gantner, MBBS; Alisa M. Higgins, MPH; Olivier Huet, MD, PhD; Jessica Kasza, PhD; Lynne Murray, BAppSci; Lynette Newby, MHSc; Jeffrey J. Presneill, MBBS, PhD; Stephen Rashford, MBBS; Jeffrey V. Rosenfeld, MD, MS; Michael Stephenson, BHSc; Shirley Vallance, MClinRes; Dinesh Varma, MD; Steven A. R. Webb, MD, PhD; Tony Trapani, BEmergHealth; Colin McArthur, MB, ChB; for the POLAR Trial Investigators and the ANZICS Clinical Trials Group

- A multicenter RCT in 6 countries
- **511 patients** both out-of-hospital and in ER after severe TBI. (2010.12.05 ~ 2018.05.15)
- **Early induction of hypothermia (33° C-35° C)** for at **least 72 hours** and **up to 7 days** if ICP were elevated, followed by **gradual rewarming**
- The primary outcome: **Favorable neurologic outcomes or independent living (GOS-Extended score, 5-8** [scale range, 1-8]) at **6 months** after injury.

RECENT META-ANALYSIS

META-ANALYSIS OF THERAPEUTIC HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY IN ADULT AND PEDIATRIC PATIENTS.

CRIT CARE MED 2017; 45:575–583

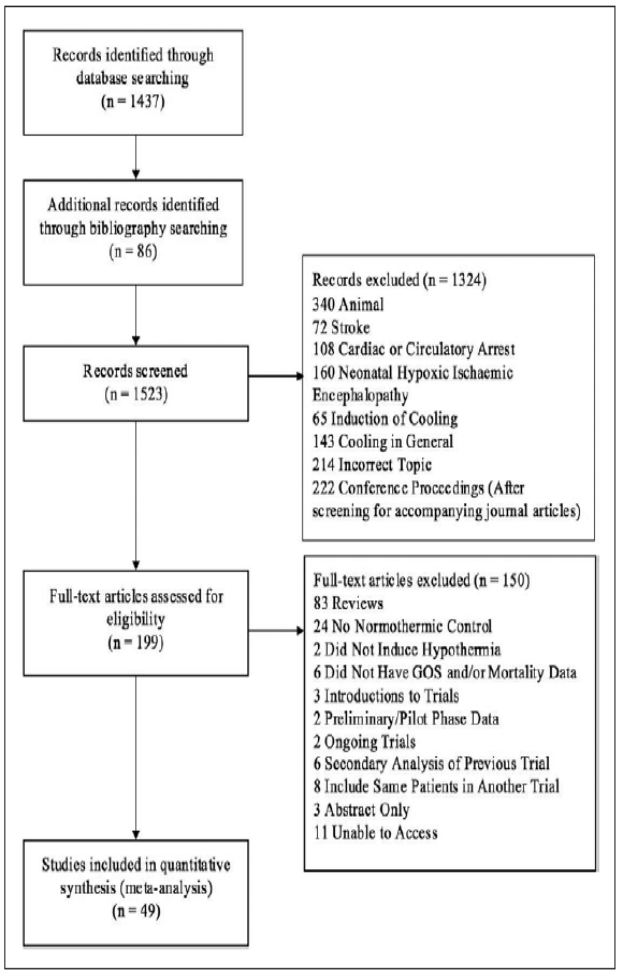


TABLE 1. Relative Benefit of Hypothermia Versus Normothermia Patients for Favorable Neurologic Outcome Within Subgroup Analyses of Adult Patients

	Effect Size		Subgroup Characteristics		Heterogeneity Level	
Analysis	Risk Ratio (95% CI)	*p*	No. of Trials	No. of Patients	χ^2 (*p*)	I^2 (%)
Induction of cooling						
Selective brain cooling	2.36 (1.35–4.12)	0.003	2	77	0.91 (0.34)	0
Systemic cooling	1.30 (1.14–1.48)	0.0001	31	2,959	62.90 (0.0004)	52
Target temperature						
Moderate (below 33°C)	1.35 (1.06–1.70)	0.01	14	1,496	31.9 (0.002)	59
Mild (above 33°C)	1.33 (1.12–1.57)	0.0009	19	1,423	35.57 (0.008)	49
Duration, hr						
24	1.51 (1.11–2.06)	0.009	5	282	0.38 (0.98)	0
48	0.93 (0.75–1.16)	0.54	10	1,083	15.72 (0.07)	43
72	1.61 (1.32–1.96)	0.00001	5	308	1.53 (0.82)	0
>72	1.41 (1.09–1.82)	0.009	7	610	11.26 (0.08)	47
Rewarming rate						
Natural	1.52 (1.29–1.78)	0.00001	7	573	4.06 (0.67)	0
1°C every 1–6 hr	1.24 (0.95–1.61)	0.11	9	1,482	28.42 (0.0004)	72
1°C every 12–24 hr	1.14 (0.82–1.59)	0.42	9	522	17.66 (0.02)	55
Intracranial pressure cointerventions						
Barbiturates	1.02 (0.83–1.25)	0.87	12	1,273	22.67 (0.02)	51
No barbiturates	1.63 (1.35–1.97)	0.00001	12	641	3.65 (0.98)	0
Decompressive craniectomy/craniotomy	1.43 (1.13–1.82)	0.003	7	496	10.92 (0.09)	45
No decompressive craniectomy/craniotomy	1.21 (0.98–1.48)	0.07	18	1,521	33.64 (0.009)	49
CSF drainage	1.11 (0.87–1.40)	0.40	11	914	20.59 (0.02)	51
No CSF drainage	1.44 (1.14–1.81)	0.002	12	755	18.52 (0.07)	41

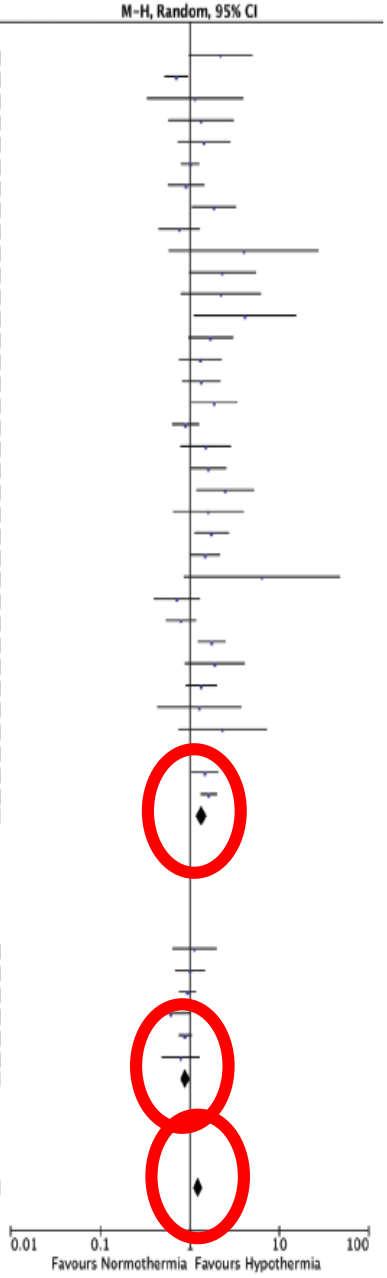
Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Adults						
Aibiki et al., 2000	1	15	3	11	0.5%	0.24 [0.03, 2.05]
Andrews et al., 2015	68	191	51	189	5.1%	1.32 [0.98, 1.79]
Chen et al., 2001	3	30	8	30	1.3%	0.38 [0.11, 1.28]
Clark et al., 1996	3	7	3	8	1.3%	1.14 [0.33, 3.94]
Clifton et al., 1992	1	5	1	5	0.4%	1.00 [0.08, 11.93]
Clifton et al., 1993	8	23	8	22	2.5%	0.96 [0.44, 2.10]
Clifton et al., 2001	53	190	48	178	4.9%	1.03 [0.74, 1.44]
Clifton et al., 2011	12	52	8	45	2.4%	1.30 [0.58, 2.89]
Gal et al., 2002	2	15	5	15	1.0%	0.40 [0.09, 1.75]
Harris et al., 2009	6	12	4	13	1.8%	1.63 [0.60, 4.38]
Hashiguchi et al., 2003	1	9	0	8	0.3%	2.70 [0.13, 58.24]
Hayashi et al., 2005	7	20	12	21	2.8%	0.61 [0.30, 1.24]
Hirayama et al., 1994	4	12	5	10	1.8%	0.67 [0.24, 1.83]
Ishikawa et al., 2000	8	41	0	50	0.3%	20.64 [1.23, 347.29]
Jiang et al., 1998	6	[illegible]	14	24	2.6%	0.45 [0.21, 0.96]
Jiang et al., 2000	11	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 1.03]
Lee et al., 2010	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] 3.55]
Liu et al., 1999	9	28	[illegible]	[illegible]	[illegible]	[illegible] 1.67]
Liu et al., 2006	11	43	12	23	3.1%	0.49 [0.26, 0.93]
Maekawa et al., 2015	33	94	11	48	3.4%	1.53 [0.85, 2.76]
Marion et al., 1993	0	20	2	20	0.3%	0.20 [0.01, 3.92]
Marion et al., 1997	9	39	10	42	2.5%	0.97 [0.44, 2.13]
Meissner et al., 2003	3	11	3	13	1.1%	1.18 [0.30, 4.72]
Nara et al., 1997	1	9	4	14	0.6%	0.39 [0.05, 2.95]
Polderman et al., 2002	40	64	52	72	5.5%	0.87 [0.68, 1.10]
Qiu et al., 2005	11	43	22	43	3.4%	0.50 [0.28, 0.90]
Qiu et al., 2007	9	40	13	40	2.7%	0.69 [0.33, 1.43]
Shiozaki et al., 1993	8	16	14	17	3.7%	0.61 [0.35, 1.04]
Shiozaki et al., 1999	0	8	0	8		Not estimable
Shiozaki et al., 2001	8	45	6	46	1.9%	1.36 [0.51, 3.62]
Smrcka et al., 2005	5	35	11	37	1.9%	0.48 [0.19, 1.24]
Soukup et al., 2002	5	29	12	22	2.1%	0.32 [0.13, 0.77]
Suehiro et al., 2014	16	47	31	129	3.9%	1.42 [0.86, 2.34]
Tokutomi et al., 2004	25	31	13	33	4.1%	2.05 [1.30, 3.23]
Yamamoto et al., 2002	4	22	9	17	1.8%	0.34 [0.13, 0.93]
Yan et al., 2010	23	73	29	75	4.2%	0.81 [0.52, 1.27]
Zhao et al., 2011	1	40	4	41	0.5%	0.26 [0.03, 2.19]
Zhi et al., 2003	51	198	72	198	5.1%	0.71 [0.52, 0.96]
Zhu et al., 2003	23	58	31	58	4.5%	0.74 [0.50, 1.10]
Subtotal (95% CI)		**1710**		**1716**	**92.0%**	**0.82 [0.70, 0.96]**
Total events	491		565			
Heterogeneity: Tau² = 0.09; Chi² = 72.53, df = 37 (P = 0.0004); I² = 49%						
Test for overall effect: Z = 2.44 (P = 0.01)						
2.2.2 Children						
Adelson et al., 2005	5	32	7	36	1.7%	0.80 [0.28, 2.28]
Adelson et al., 2013	6	38	2	38	0.9%	3.00 [0.65, 13.94]
Beca et al., 2015	[illegible]	24	1	[illegible]	[illegible]	3.25 [0.36, 29.16]
Biswas et al., 2002	3	10	0	[illegible]	[illegible]	[illegible] 13.[illegible]
Bourdages et al., 2010	3	[illegible]	1	9	0.6%	3.8[illegible] [illegible] 25.5]
Hutchison et al., 2008	[illegible]	102	4	3	[illegible]	1.[illegible] [illegible] 1.04]
Li et al., 2009	1	12	2	10	0.5%	0.42 [0.04, 3.95]
Salonia et al., 2010	3	19	0	15	0.3%	5.60 [0.31, 100.70]
Subtotal (95% CI)		**244**		**248**	**8.0%**	**1.66 [1.06, 2.59]**
Total events	47		27			
Heterogeneity: Tau² = 0.00; Chi² = 6.75, df = 7 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)		**1954**		**1964**	**100.0%**	**0.87 [0.74, 1.01]**
Total events	538		592			
Heterogeneity: Tau² = 0.11; Chi² = 86.91, df = 45 (P = 0.0002); I² = 48%						
Test for overall effect: Z = 1.78 (P = 0.08)						
Test for subgroup differences: Chi² = 8.38, df = 1 (P = 0.004), I² = 88.1%						

Adults

Children

Figure 3. Relative risk of mortality in the hypothermia treatment group versus normothermia group for adult and pediatric studies.

Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Adults						
Aibiki et al., 2000	12	15	4	11	1.5%	2.20 [0.97, 5.00]
Andrews et al., 2015	49	191	69	189	3.8%	0.70 [0.52, 0.95]
Clark et al., 1996	3	7	3	8	0.8%	1.14 [0.33, 3.94]
Clifton et al., 1992	4	5	3	5	1.5%	1.33 [0.58, 3.09]
Clifton et al., 1993	12	23	8	22	1.9%	1.43 [0.73, 2.82]
Clifton et al., 2001	82	190	76	178	4.2%	1.01 [0.80, 1.28]
Clifton et al., 2011	21	52	20	45	2.9%	0.91 [0.57, 1.45]
Gal et al., 2002	13	15	7	15	2.3%	1.86 [1.04, 3.30]
Hashiguchi et al., 2003	6	9	7	8	2.5%	0.76 [0.45, 1.30]
Hayashi et al., 2002	4	7	1	7	0.4%	4.00 [0.58, 27.41]
Hayashi et al., 2005	11	20	5	21	1.4%	2.31 [0.98, 5.47]
Hirayama et al., 1994	8	12	3	10	1.1%	2.22 [0.80, 6.21]
Idris et al., 2014	[illegible]	19	2	[illegible]	0.7%	4.11 [1.10, 15.37]
Jiang et al., 2000	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.71 [0.96, 3.04]
Lee et al., 2010	[illegible]	[illegible]	[illegible]	[illegible]	2.4%	1.31 [0.75, 2.29]
Liu et al., 1999	17	[illegible]	[illegible]	[illegible]	[illegible]	1.34 [0.82, 2.19]
Liu et al., 2006	28	43	8	23	2.2%	1.87 [1.03, 3.41]
Maekawa et al., 2015	44	94	25	48	3.6%	0.90 [0.64, 1.27]
Marion et al., 1993	12	20	8	20	2.1%	1.50 [0.79, 2.86]
Marion et al., 1997	24	39	16	42	2.9%	1.62 [1.02, 2.55]
Nara et al., 1997	8	9	5	14	1.7%	2.49 [1.19, 5.22]
Polderman et al., 2002	10	64	7	72	1.3%	1.61 [0.65, 3.97]
Qiu et al., 2005	28	43	16	43	3.0%	1.75 [1.12, 2.73]
Qiu et al., 2007	28	40	19	40	3.3%	1.47 [1.00, 2.16]
Shiozaki et al., 1993	6	16	1	17	0.3%	6.38 [0.86, 47.29]
Shiozaki et al., 1999	5	8	7	8	2.3%	0.71 [0.39, 1.30]
Shiozaki et al., 2001	21	45	27	46	3.3%	0.80 [0.54, 1.18]
Smrcka et al., 2005	30	35	18	37	3.5%	1.76 [1.23, 2.52]
Soukup et al., 2002	15	29	6	22	1.7%	1.90 [0.88, 4.09]
Suehiro et al., 2014	21	47	43	129	3.2%	1.34 [0.90, 2.00]
Tokutomi et al., 2004	6	31	5	33	1.0%	1.28 [0.43, 3.76]
Yamamoto et al., 2002	9	22	3	17	0.9%	2.32 [0.74, 7.27]
Yan et al., 2010	30	73	28	75	3.2%	1.10 [0.74, 1.65]
Zhao et al., 2011	30	40	21	41	3.5%	1.46 [1.03, 2.07]
Zhi et al., 2003	122	198	75	198	4.4%	1.63 [1.32, 2.01]
Subtotal (95% CI)		**1561**		**1548**	**80.0%**	**1.35 [1.18, 1.54]**
Total events	770		580			
Heterogeneity: Tau² = 0.07; Chi² = 71.60, df = 34 (P = 0.0002); I² = 53%						
Test for overall effect: Z = 4.48 (P < 0.00001)						
2.1.2 Children						
Adelson et al., 2005	14	32	14	36	2.4%	1.13 [0.64, 1.98]
Adelson et al., 2013	22	38	22	38	3.3%	1.00 [0.68, 1.47]
Beca et al., 2015	[illegible]	24	23	26	4.3%	0.94 [0.75, 1.18]
Biswas et al., 2002	[illegible]	10	1	11	[illegible]	[illegible] 0.37, 1.02]
Hutchison et al., 20[illegible]	[illegible]	[illegible]	8[illegible]	[illegible]	4[illegible]	0.8[illegible] 0.75, 1.04]
Salonia et al., 2010	11	19	11	15	2.7%	0.79 [0.48, 1.29]
Subtotal (95% CI)		**225**		**229**	**20.0%**	**0.90 [0.80, 1.01]**
Total events	143		161			
Heterogeneity: Tau² = 0.00; Chi² = 3.52, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		**1786**		**1777**	**100.0%**	**1.24 [1.10, 1.40]**
Total events	913		741			
Heterogeneity: Tau² = 0.08; Chi² = 102.66, df = 40 (P < 0.00001); I² = 61%						
Test for overall effect: Z = 3.53 (P = 0.0004)						
Test for subgroup differences: Chi² = 20.97, df = 1 (P < 0.00001), I² = 95.2%						



Adults

Children

Figure 2. Risk ratio of favorable neurologic outcome in the hypothermia treatment group versus normothermia group for adult and pediatric studies.

META-ANALYSIS OF THERAPEUTIC HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY IN ADULT AND PEDIATRIC PATIENTS. *CRIT CARE MED 2017; 45:575–583*

- **18% reduction in mortality** (RR, 0.82; 95% CI, 0.70–0.96; $p = 0.01$)
- **35% improvement in neurologic outcome** (RR, 1.35; 95% CI, 1.18–1.54; $p < 0.001$).
- **"The optimal management strategy** for adult patients included cooling patients to **selective brain cooling, a minimum of 33° C for 72 hours, followed by spontaneous, natural rewarming."**
- **Adverse outcomes** were observed **in children** who underwent hypothermic treatment with
  - **a 66% increase in mortality** (RR, 1.66; 95% CI, 1.06–2.59; $p = 0.03$)
  - **a marginal deterioration of neurologic outcome** (RR, 0.90; 95% CI, 0.80–1.01; $p = 0.06$).
- **Conclusions:** Therapeutic hypothermia is **likely a beneficial treatment following traumatic brain injuries in adults** but **cannot be recommended in children.**

THERAPEUTIC WHOLE-BODY HYPOTHERMIA REDUCES DEATH IN SEVERE TRAUMATIC BRAIN INJURY IF THE COOLING INDEX IS SUFFICIENTLY HIGH

: META-ANALYSES OF THE EFFECT OF SINGLE COOLING PARAMETERS AND THEIR INTEGRATED MEASURE.

J NEUROTRAUMA. 2018 OCT 15;35(20):2407-2417.

- **We extracted data on TBI severity, body temperature, death, and cooling parameters**; then we calculated **the cooling index, an integrated measure of therapeutic hypothermia**.
- **As independent factors, milder and longer cooling, and rewarming at <0.25° C/h were associated with better outcome.**
- **Therapeutic hypothermia was beneficial only if the cooling index (measure of combination of cooling parameters) was sufficiently high.**
- By analyzing methodologically homogenous studies, we show that **"Cooling improves the outcome of severe TBI", and this beneficial effect depends on certain cooling parameters and on their integrated measure, the cooling index.**

BRAIN TRAUMA FOUNDATION GUIDELINES 4TH ED

Prophylactic Hypothermia

- Not significantly associated with decreased mortality when compared with normothermic controls.
- Target temperature 32-33 ℃ or >33 ℃
- Rewarming 1degress/hr
- However, preliminary findings suggest that a greater decreased in mortality risk is observed when target temperatures are maintained for more than 48hrs(III)

Changed Level Ⅲ to ⅡB

Level Ⅱ B

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

DISCUSSION

- Induced hypothermia protocol

  ;target temperature, cooling time, rewarming time

  patient selection, cooling method
- Treatment target

  ;intracranial pressure
- Prognosis ; lowering ICP not means prognosis
- Pathophysiology and multi-factorial monitoring
- Cardiac arrest vs diffuse brain injury vs focal ecacuated mass???

IN THE FUTURES

- World wide RCT with standard protocols

  based on effectiveness results at animal models
- More detailed monitoring for perfusion, ICP, blood flow, O2 saturation etc
- Developed more safer induction, maintenance and rewarming techniques
- Combined management with variable neuroprotective agents
- Prehospital hypothermic induction manuals

Thank you