MMS施行手順

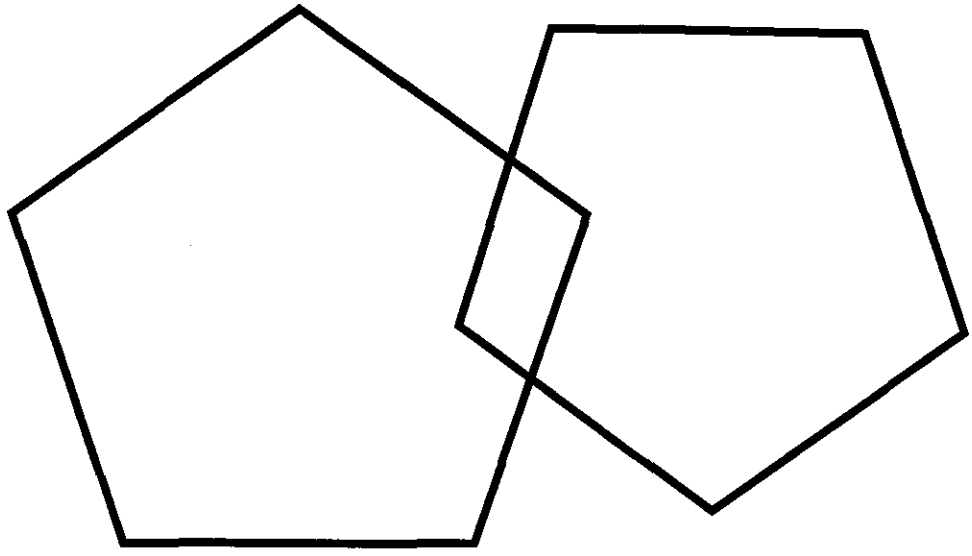
1. 時と所の見当識	a.今日は何年の、何月何日ですか。 b.今の季節は何でしょう。 c.今は何時ごろですか。 d.ここはどこですか。 県・市・病院名・科名・フロア	3点 低下順→日→年→月→季節→時刻 1点　暦上ではなく四季 1点　1時間くらいのずれは可 全部で5点　状況・場所に応じて変更可
2. 記銘	「みかん」「電車」「27」 3単語を連続して1秒間隔で聞かせ、復唱 復唱できない場合には3回程度を目安に 繰り返す 復唱後、「5分後にもう一度思いだしてもらうので、覚えておくように」と教示。	全問正解で3点 1単語1点 1回目の正答だけ採点 代替問題 「リンゴ」「車」「35」
3. Serial 7	「100から順に7を引いて下さい」 引く数・元の数は聞き返されても再教示はしない。(「なんだったでしょうね」) 思い出せない時は中止 誤りがあっても5回まで続ける。	1回毎の引き算の正答ひとつに1点 93-86-79-72-65　までいえて最高5点 (例;「93-86-80-73-70」なら3点)
4. 想起	No.2で覚えた単語の5分後想起	正答1語に1点(全問正解3点)
5. 呼称	「鉛筆」「時計」(身近な日用品)実物を 見せて「これはなんですか？」 日本語でない場合は「日本語では？」	正答1つに1点(全問正解2点) 日本語で正しく答えられなければ誤答
6. 復唱	「私の言ったとおりに、そのまま真似をして言ってください」 「ちりもつもればやまとなる」	正しく復唱できれば1点
7. 口頭命令	被験者の前に大(B5;右側)、小(B6; 左側)を置く。「この紙を使って、私の指示する通りにして下さい。1回しか言いませんから、言い終わってからすぐに指示されたことを始めてください。」 ゆっくりと「大きいほうの紙を手に取り、それを半分に折って、私に渡してください」 「××でしたか？」と確認を求めてきても 「言われた通りにしてください。」と言って 再教示しない	各段階ごとに、指示されたことが正しく行えれば、1点(全問正解3点)
8. 書字命令	「目を閉じてください」と書いてある紙をみせ 「この紙に書いてある通りに○○さんが 動作をしてみせて下さい」	正しく動作ができれば1点
9. 文を書く	「今、○○さんはここで何をしているのかを簡単な文章で書いてください」 手紙に「お元気」と書くか、「お元気ですか」と書くかを聞くと文を書くことが可能になる場合がある	文章であれば内容は問わない。 主語がなくても述語があれば可。 単語だけでは不可。そのときは励まして、最後まで書くよう促す。 当て字、送り仮名の誤りは減点しない。 偏・つくり・濁点の誤りは2ヵ所で誤字1字とみなす。 文全体で1字以内の誤りは可。 正答　1点
10. 五角形模写	手本を示して、見えるとおりに模写を指示する	二つの五角形が、一部重なって描ければよい。これを満たせば1点 形の崩れは厳密にはみない。 平行位置は×。

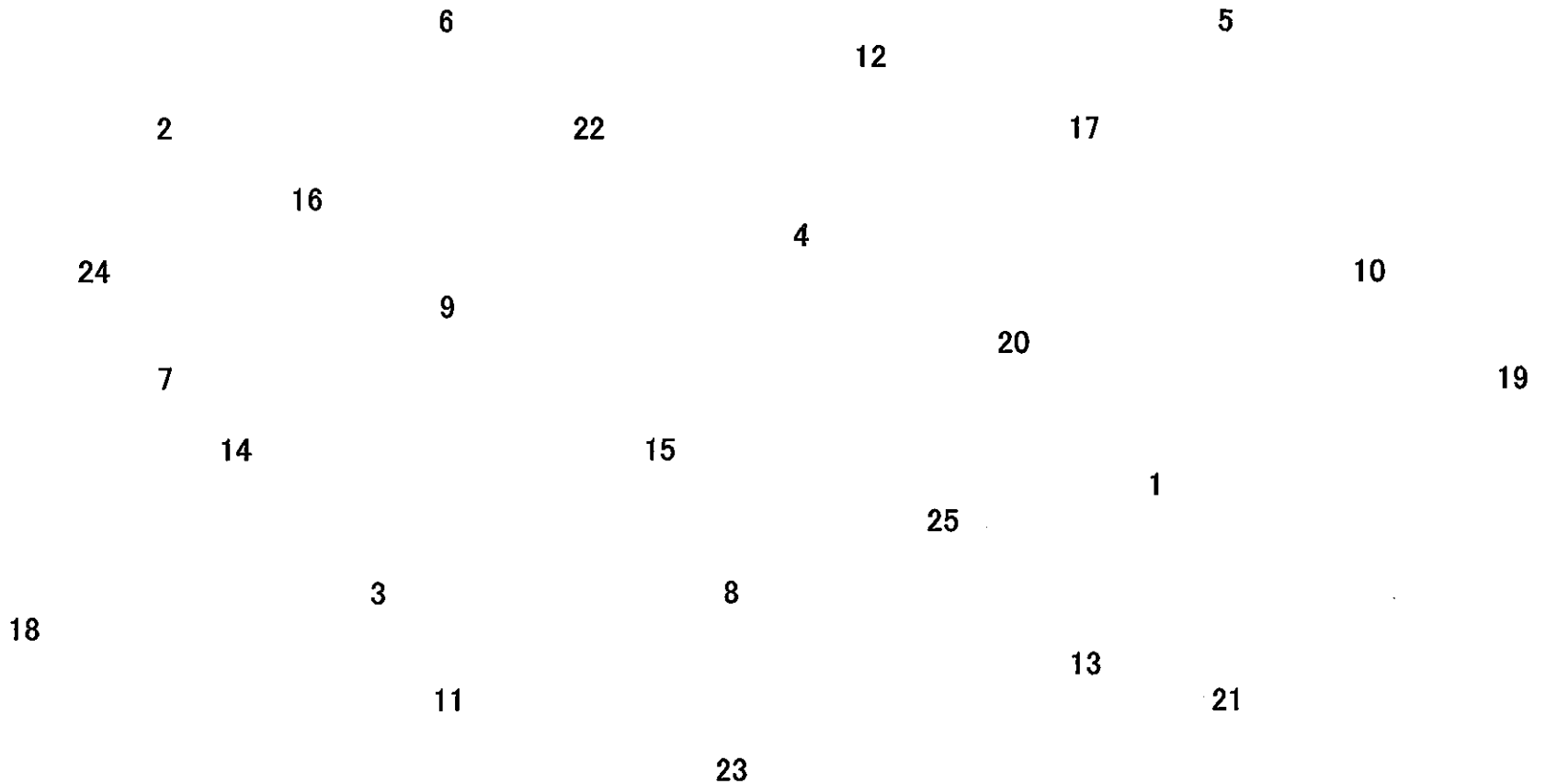
満点:30点　総合判定　24点～　正常範囲
15～23点　中等度低下
～14点　高度低下

MMS;order

目を閉じて下さい（めをとじてください）

MMS;pentagon

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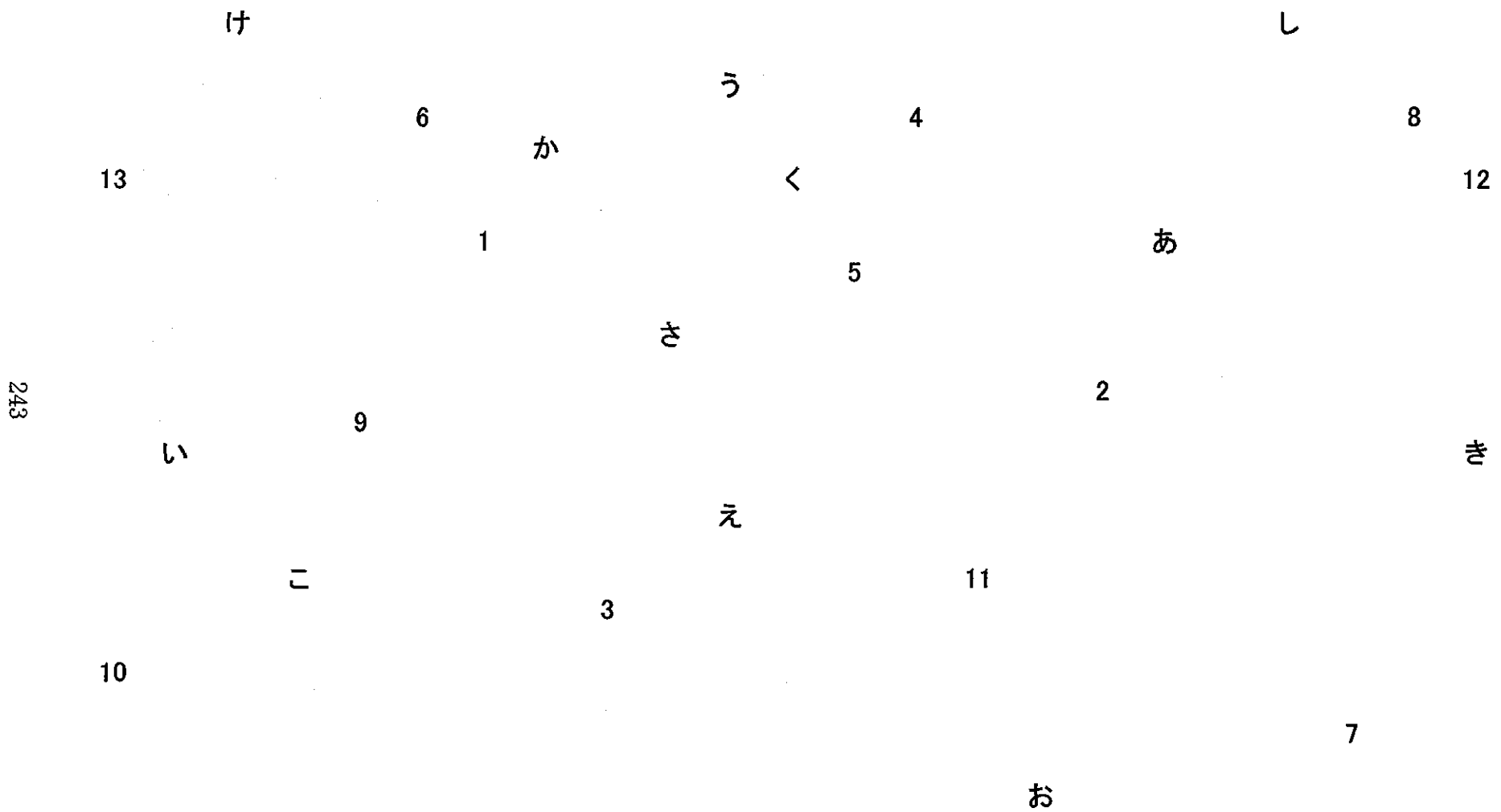
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Ⅳ．研究成果の刊行に関する一覧表

書籍

著者名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Maekawa T, Hayashi N, Ogino K, Takezawa J, Nagao S, Ohashi Y, Yamashita S, Okabayashi K	A randomized controlled trial of therapeutic hypothermia in severe head-injured patients in Japan : Overview of the protocol.	Hayashi N, Bullock R, Dietrich DW, Maekawa T, Tamura A	Hypothermia for acute brain damage pathomechanism and practical aspects.	Springer-Verlag	Tokyo	2004	246-250

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Hypothermia for Acute Brain Damage: Pathomechanism and Practical Aspects

Springer

A Randomized Controlled Trial of Therapeutic Hypothermia in Severe Head-Injured Patients in Japan: Overview of the Protocol

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Summary. Protection against brain insults is one of the most difficult aspects of clinical practice. Recently, mild hypothermia has been applied to cardiopulmonary resuscitated victims and brain-protective effects were proved by two randomized, controlled trials (RCT). Clifton's group applied mild hypothermia therapy in severe head-injured cases (Glasgow Coma Scale; GCS < 8), but failed to prove any effectiveness. Our aim is to apply mild hypothermia therapy as a RCT in 300 traumatic brain injury cases in 40 medical centers in Japan. Inclusion criteria are: (1) GCS 4–8, except best motor response of 6; (2) core body temperature must be reduced to less than 35.5°C at 6 h after head injury in the mild hypothermia group; (3) age ≤ 15 to <70 years old. Patients are randomized into either a control group (35.5°–37.0°C, 100 patients) or a mild hypothermia group (32.0°–34.0°C, 200 patients). Core body temperature must be controlled for at least 72 h in the two groups and may be prolonged, if necessary. Brain-oriented intensive care is required; physiologic parameters are qualified by cardiac index, as well as internal jugular venous oxygen saturation and temperature, which are recorded and stored in a computer in every 1 min. Evaluations of the effect of mild hypothermia therapy are carried out using the Glasgow Outcome Scale at 3 and 6 months, and by biochemical parameters such as cytokines, free radical products, and neurotoxic excitatory amino acids between the two groups. At this point in time, 74 patients have been enrolled.

Key words: Therapeutic hypothermia, Traumatic brain injury, Internal jugular venous oxygen saturation, Glasgow Outcome Scale, Neurochemicals

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Introduction

The pathophysiologic mechanisms responsible for damaging the brain following severe traumatic brain injury (TBI) are multiple, such as glutamate excitotoxicity, intracellular Ca^{2+} overload, free radicals, cytokines and so on, besides the ordinary mechanisms [1]. On the other hand, therapeutic strategies are very poor from the clinical point of view.

Recently, animal experiments have provided persuasive evidence that mild hypothermia confers significant protection against ischemic or traumatic brain insults [2]. In contrast to hypothermia, slight elevation of brain temperature worsened the outcome and very high brain temperature (up to 43.8°C) was actually recorded [3]. Based on these facts, clinical application of therapeutic mild hypothermia has been applied to stroke, severe head-injured, and cardiac arrest-resuscitated victims. The effectiveness of therapeutic mild hypothermia was proven by two randomized controlled trials (RCT) in cardiac arrest-resuscitated patients [4,5].

In severe TBI patients, more than 45 potentially relevant articles have been published [6–8]. Among these clinical trials and their meta-analyses [9], none could prove the effectiveness of mild hypothermia therapy based on neurological outcome. The reasons for failure are not clear, but they seem to the similar to those of brain protection/resuscitation therapy by barbiturate coma. In this report, our RCT of mild hypothermia therapy in severe TBI patients (Glasgow Coma Scale; GCS 4–8) in Japan is introduced.

Brief Overview of the Protocol

Our primary hypothesis is that mild hypothermia for at least 72 h in TBI patients will improve neurological outcome at 3 and 6 months as quantified by the Glasgow Outcome Scale (GOS) score and high brain performance functions at 6 months evaluated by the Mini-Mental Statement, Trial Making Test B, and animal naming test, as compared with antihypothermia (normothermia). It is our secondary hypothesis that mild hypothermia will also improve neuro-pathophysiological events as assessed by cerebrospinal fluid (CSF) excitatory amino acids, free radical-related molecules, and cytokines in a limited number of the patients.

Our RCT investigators consist of four clinicians, an epidemiologist, and a biostatistician. Forty centers, mainly university emergency and critical care medical centers, are involved. Three hundred patients who have been admitted with TBI within 6 h following the insults will be enrolled. Inclusion and exclusion criteria are shown in Table 1. Statistical design and sample size calculations are as follows. The RCT is designed to achieve a power of 0.90 and alpha = 0.05 (two-sided) to detect an improvement of 20% in the number of patients with GOS (good outcome plus moderately disabled). Patients are randomized by a 24-h internet allocation system developed by the University Medical Information Network (Tokyo University, Tokyo). The allocation is done by a modified minimization method using each medical center, age (more than 45 or less than or equal to 45 years old), and GCS (4–5 or 6–8) as adjustment variables. The allocation of the patients is shown in Table 2. Neurological outcome evaluated by GOS at 3 and 6 months following TBI will be analyzed when the entry number of the patients reaches 150 (primary research). If a significant effect cannot be obtained, the protocol will be continued with different anesthesia methods, from midazolam and analgesics to neuroleptics. If an effect is then obtained, the protocol will be changed to evaluate the difference between the two anesthesia methods with the effective temperature, either 32.0°–34.0°C or 35.5°–37.0°C (secondary research, Table 2).

TABLE 1. Inclusion and exclusion criteria for therapeutic hypothermia in our protocol

Inclusion criteria

1. Glasgow Coma Scale (GCS) score 4–8, except a case of best motor response = 6
2. Age is ⩾15 and <70 years old
3. Either male or female
4. Informed or waiver of consent required

Exclusion criteria

1. Persistent hypotension; systolic blood pressure <90 mmHg
2. Platelet count <50 000/μl
3. Severe liver and/or renal failure
4. Acute myocardial infarction, heart failure, or severe arrhythmia
5. Pregnancy or suspected pregnancy
6. Deep drunkenness
7. Severe penetrating brain injury
8. Suspected good neurological outcome by hematoma evacuation
9. Core body temperature less than 30°C on admission
10. Difficult to adapt to mild hypothermia

TABLE 2. Sample size, grouping, and anesthesia methods

Primary research				
150 cases		Hypothermia M (Midazolam) group	32.0°–34.0°C	100 cases
4 ⩽ GCS ⩽ 8		Control M (Midazolam) group	35.5°–37.0°C	50 cases
Secondary research				
Primary research	150 cases	Hypothermia NLA group	32.0°–34.0°C	100 cases
is not significant	4 ⩽ GCS ⩽ 8	Control NLA group	35.5°–37.0°C	50 cases
Primary research	150 cases	Effective temp. M group		75 cases
is significant	4 ⩽ GCS ⩽ 8	Effective temp. NLA group		75 cases

Registration: 300 cases (24 h applicable using UMIN).
UMIN, University Medical Information Network in Japan; GCS, Glasgow Coma Scale score; NLA, Neurolept analgesia using droperidol and fentanyl.

Midazolam and analgesics with chlorpromazine, or droperidol and fentanyl, are used with nondepolarizing muscle relaxants (pancuronium or vecuronium). In the mild hypothermia and control groups, core body temperature is kept at 32.0°-34.0°C and 35.5°–37.0°C, respectively, for at least 72 h. In the mild hypothermia group, it is preferred that core body temperature be less than 35.5°C at 6 h after TBI, and it is permitted to maintain hypothermia for at least 72 h, if required from a clinical point of view.

In addition to ordinary monitoring, special data are collected such as core body temperature (measured in the brain, internal jugular vein, pulmonary artery, or bladder), internal jugular venous oxygen saturation (Q2 continuous cardiac output/SO2 Computer and a catheter; Abbott Laboratories, North Chicago, IL, USA), cardiac index, and mixed venous oxygen saturation (Vigilance CEDV and a catheter; Edwards Life Sciences, Irvine, CA, USA), which are collected every 1 min and stored in a computer until 72 h following the onset of TBI. Intracranial or cerebrospinal fluid pressure is also monitored, if possible. Brain-oriented intensive care (Table 3) is required. Cessation of the mild hypothermia is very important, this being decided upon by brain computed tomography and/or intracranial pressure. Rewarming in the hypothermia group is allowed 72 h after the onset of TBI. The patients should not be warmed, but the degree of cooling tapered off (less than 0.1°C/h), usually

TABLE 3. Brain-oriented intensive care

Respiration
- PaO_2 > 150 mmHg, or around 100 mmHg (long term)
- Neurogenic pulmonary edema: 3–5 cm PEEP and head-up tilt
- $PaCO_2$ = 35–40 mmHg
  - change by internal jugular venous oxygen saturation or by intracranial pressure
- Prevent fighting against the ventilator and excessive body movements

Circulation
- Cerebral perfusion pressure = 60–100 mmHg
  - relatively low in head-injured patients
  - relatively high in hypertensive patients
- Antiarrhythmia
  - lidocaine: 1–2 mg kg^{-1}, propranolol: 1 mg (total dose ≤10 mg)
- Prevention of hypotension
  - volume load with plasma expanders without glucose
  - dopamine: 2–15 $\mu g\,kg^{-1}\,min^{-1}$, dobutamine: 2–15 $\mu g\,kg^{-1}\,min^{-1}$
  - (avoid persistent peripheral vasoconstriction)
- Prevention of hypertension
  - Ca-blocker (may cause intracranial hyperemia, hence intracranial hypertension)
    - diltiazem: 2 mg i.v., 5–15 $\mu g\,kg^{-1}\,min^{-1}$
    - nicardipine: 10–20 $\mu g\,kg^{-1}$ i.v., 0.3–3.0 kg min^{-1}
- Prevent intracranial hypertension: <20 mmHg
- Hemodilution
  - Ht = 30%–50%, Hb = 10–12 g dl^{-1}
- Head-up tilt position
  - 10°–30°
- Prevent excessive neck rotation, flexion, and extension

Metabolism
- Plasma glucose
  - 120–140 mg dl^{-1}, prevent hyperglycemia and hypoglycemia
- Fluid management
  - electrolyte solution: 30–50 ml $kg^{-1}day^{-1}$
  - pH: 7.3–7.5, Na^+: 135–145 mEq l^{-1}, K^+: 3.5–5.0 mEq l^{-1}
  - Ca^{2+}: 2.0–2.6 mEq l^{-1}, Mg^{2+}: 0.98–1.14 mEq l^{-1} (Mg: 1.4–2.6 mg l^{-1})
  - serum osmolality: 280–320 mOsm l^{-1}
  - colloid osmotic pressure >15 mmHg, albumin >4 g dl^{-1}
- Nutrition
  - start nasointestinal tube feeding at early days: 30–50 kcal $kg^{-1}\,day^{-1}$
  - prevent stress-induced gastric ulcer
- Body temperature: 35.5°–37.0°C
  - mild hypothermia preferred for severe cases (32.0°–34.0°C)
- Seizure: diazepam 0.2 mg kg^{-1}, or thiopental 2–5 mg kg^{-1}

PEEP, positive end-expiratory pressure.

taking a few days. Thereafter, core body temperature is kept below 37.0°C until day 7 after TBI. Brain computed tomography is taken to assess and report on admission and at 7 ± 1 days.

Patients are examined daily for 2 days, on day 3, 1 day before warming, and 1–2 days after rewarming. Glasgow Outcome Scale at days 7 and 30, and at 3 and 6 months, will be assessed. The physician taking part in the RCT cannot be blinded, but the individual responsible for all neurological outcome assessments will be completely blinded. Primary end points will

be evaluated by GOS at 3 and 6 months, and high brain performance functions at 6 months following TBI. Secondary end points will be evaluated by GCS at 7 and 30 days and by physiologic parameters, such as cardiac index, mixed venous oxygen saturation, and internal jugular venous oxygen saturation. Neuropathological molecules, such as excitatory amino acids (glutamate and aspartate), free radical-related molecules (NO_2^-, NO_3^-, nitrotyrosine, 8-hydroxy-2′-deoxyguanosine), and cytokines (tumor necrosis factor-α, interleukin-6, interleukin-10, interleukin-8, granulocyte/monocyte colony-stimulating factor, interferon-γ) in cerebrospinal fluid, blood, or urine will be measured in a limited number of the patients in each group. At this point in time, 74 patients have been enrolled.

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