Clinical Neurology and Neurosurgery 123 (2014) 181–186

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Therapeutic hypothermia for adult community-acquired bacterial meningitis—Historical control study

Marko Kutleša [a,*], Dragan Lepur [b], Bruno Baršić [a]

[a] University of Zagreb, School of Medicine, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Department of Intensive Care Medicine and Neuroinfectology, Zagreb, Croatia
[b] University of Zagreb, School of Dental Medicine, Department of Intensive Care Medicine and Neuroinfectology, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, Croatia

ARTICLE INFO

Article history:
Received 4 April 2014
Received in revised form 3 May 2014
Accepted 22 May 2014
Available online 2 June 2014

Keywords:
Therapeutic hypothermia
Bacterial meningitis
Clinical outcome

ABSTRACT

Objective: Despite advances in antibiotic therapy and critical care, community-acquired bacterial meningitis (CABM) continues to have poor outcome in a significant portion of patients. This study was designed to assess the efficacy of therapeutic hypothermia (TH) in the treatment of CABM.
Material and methods: In a period from January 2009 to January 2013, 41 enrolled patients with CABM were treated with TH. Their outcome was compared to 90 patients in the historical control group that were recruited from the existing database and included patients in a period between 1994 and 2008 with Glasgow coma scale score (GCS) ≤9 and respiratory failure. TH was indicated in patients with GCS ≤9, respiratory failure, and breath holding index ≤0.835 (measured with transcranial Doppler). If the acoustic window was absent, GCS ≤9 plus optic nerve sheath diameter of ≥6 mm plus respiratory failure were indications for TH.
Results: Outcome variables were mortality and neurologic recovery measured with the Glasgow outcome scale (GOS). The incidence of hospital mortality (19.5% vs 48.9%, $p = 0.002$) and adverse neurological outcome (GOS 1–3) (43.9% vs 65.6%, $p = 0.023$) were significantly lower in patients treated with TH. Multivariate analysis confirmed the positive effect of TH on hospital mortality (OR = 0.059, 95% CI 0.017–0.211) and risk of adverse neurological outcome (OR = 0.209, 95% CI 0.082–0.534) after an adjustment for other risk factors of unfavorable patients' outcome.
Conclusions: The new therapeutic concept based on hypothermia significantly improves the outcome in adult patients with severe CABM.

1. Introduction

Despite advances in antibiotic therapy and critical care, community-acquired bacterial meningitis (CABM) continues to impose high rates of morbidity and mortality [1–4]. Given that bacterial meningitis is frequently associated with poor outcomes, new treatment strategies are needed.

The ominous nature of intracranial hypertension (ICH) and cerebrovascular dysregulation due to vascular inflammation is crucial for adverse outcome in patients with CABM. Since the adjuvant treatment of CABM has not substantially evolved in recent years, mortality rates of CABM have mostly remained unaffected. Current treatment options are known to be of humble efficacy and might even be harmful in patients with reduced carbon dioxide vasoreactivity (CO_2R) [5,6]. In the majority (76%) of patients with severe CABM (GCS ≤9), the cerebral blood flow (CBF) chemoregulation is significantly impaired or completely lost with subsequent hypoperfusion or "luxury" perfusion [7]. In addition, the reduced CO_2R was confirmed as an accurate predictor of adverse outcome in patients with CABM [7]. Furthermore, the effect of dexamethasone on mortality in adult patients with pneumococcal meningitis has remained controversial [8,9].

Adjuvant treatment with therapeutic hypothermia (TH) for patients with severe CABM is of particular interest because it has well documented neuroprotective effects. Amongst others, it is very effective in reducing ICH and improving cerebral perfusion pressure [10,11]. Our previously reported results indicate a favorable effect of TH in patients with CABM [12]. Recently

* Corresponding author at: Department of Intensive Care Medicine and Neuroinfectology, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Mirogojska 8, Zagreb 10000, Croatia. Tel.: +385 1 2826 253; fax: +385 1 2826 255.
E-mail addresses: mkutlesa@bfm.hr (M. Kutleša), lepurix@inet.hr (D. Lepur), bbarsic@bfm.hr (B. Baršić).

http://dx.doi.org/10.1016/j.clineuro.2014.05.018
0303-8467/

published randomized control trial argues that TH lacks positive impact on the outcome of patients with CABM [13]. The main objective of this study was to assess if TH decreases mortality and improves neurological outcomes in patients with CABM.

2. Materials and methods

2.1. Patients

The patients admitted for CABM to the adult ICU at our institution were prospectively enrolled and followed the TH treatment group (TH group). The inclusion criteria were as follows: age was 18 years and older, respiratory failure with mechanical ventilation and reduced CO_2R with breath holding index (BHI) $\leq$0.835 (measured with transcranial Doppler) as accurate predictor of the adverse outcome in CABM [7], and Glasgow coma scale (GCS) score $\leq$9. If the temporal bone acoustic window was absent, the alternative inclusion criteria included GCS score $\leq$9 plus optic nerve sheath diameter (ONSD) $\geq$6 mm plus respiratory failure with mechanical ventilation. The exclusion criteria included the presence of immunosuppression (immunosuppressive drug treatment, splenectomy, human immunodeficency virus, and hematologic malignancy), brain abscess, subdural empyema, and cerebral venous sinus thrombosis.

The historic control group was recruited from a prospectively collected database of patients with CABM. Only patients with GCS score $\leq$9 and respiratory failure requiring mechanical ventilation were included in the control group in order to increase the compatibility between groups.

The patients with neurolgical symptoms that lasted for more than 48 h and have not recieved antimicrobial treatment during that period were excluded from further analysis.

2.2. Methods

2.2.1. Transcranial Doppler ultrasound (TCD)

TCD measurement of CO_2 reactivity (CO_2R) was performed by using a Multidop 4X (DWL, Sipplingen, Germany) with two 2-MHz pulsed wave probes 1.7 cm in diameter. The software used was TCD-8 for MDX (Version 8.0, Aaslid Rune).

The left and right middle cerebral arteries (MCA) were insonated simultaneously through the temporal bone windows at a depth of 50–55 mm. The probes were secured to the head of the patient with a specially designed spectacle frame that permitted a constant angle of insonation. CO_2 reactivity (CO_2R) was assessed using the breath-holding method (disconnection from the ventilator for 30 s in a deeply sedated and relaxed patient). The breath-holding index (BHI) was calculated by dividing the percentage of mean blood flow velocities (MBFV) increase during breath holding by the time (in seconds) of apnea. The measurements were made daily until recovery of CO_2 reactivity.

2.2.2. Optic nerve sheath diameter measurement

ONSD measurements were made using a B-scan ultrasound with a 10 MHz linear probe (Accuson CV70, Siemens Medical Solutions Inc., WA, USA) before and during the induced hypothermia. ONSD measurement was perfomed 3 mm behind the optic nerve papilla with the ultrasound probe on the closed upper eyelid. Optic nerve sheath diameter has been shown to be a very reliable measure of intracranial pressure (ICP). In adults, ONSD greater than 5.8 mm indicated intracranial pressure of more than 20 mm Hg [14].

2.3. Treatment

2.3.1. Therapeutic hypothermia

We used an internal protocol designed to achieve mild hypothermia (rectal temperature of 32–34 °C). Hypothermia was induced by intravenous infusion of cold (+4 °C to +8 °C) isotonic saline (2000 ml/1 h) and maintained with continuous veno-venous hemofiltration (CVVHF) by using a Prismaflex (Gambro Dasco S.p. A, Medolla, Italy) machine for 72–96 h. The blood flow rate was set to 150 ml/min, ultrafiltration rate (UFR) to 0 ml/h, and the replacement solution rate was set to 2000 ml/h. Enoxaparin was used for anticoagulation of the circuit. Time from induction of TH to the treatment value of the body temperature was achieved at the fastest rate possible. Rewarming was gradual at the rate of 0.1–0.25 °C/h [15].

2.3.2. Antimicrobial treatment

The initial antimicrobial treatment consisted of ceftriaxone alone, or in combination with ampicillin. The prevalence of the penicillin resistant *Streptococcus pneumoniae* in Croatia is less than 1%.

2.4. Study design

A historical control single centre study was performed to evaluate patients with CABM treated at the ICU of the University Hospital for Infectious Diseases "Dr. Fran Mihaljevic" in Zagreb, Croatia.

The hospital Ethics Committee approved the treatment protocol, and informed consent was obtained from the relatives of all patients treated with TH.

2.5. Measurements

BHI and ONSD were monitored daily. Variables included in the analysis were age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, etiology, presence of seizures, time from consciousness impairment to appropriate antimicrobial treatment, presence of septic shock, GOS score, the duration of TH, and complications (hypertensive hydrocephalus, ishemic stroke, hospital infections). GCS was omitted from further analysis since it is an integrative part of the APACHE II score.

The patients in the TH group have not received any other treatment for brain edema and ICH and were not treated with dexamethasone. The duration of TH was guided by the CO_2R recovery but did not exceed 5 days. If there was no recovery of CO_2R by the 5th day of TH, the outcome was poor regardless of further treatment.

The primary outcome measures were hospital mortality, unfavorable outcome defined as GOS 1–3, and a 28-day survival. Considering the severity of illness, GOS 4 as well as GOS 5 were defined as the favorable outcome.

Univariate analysis tested the statistical significance of the difference in outcome variables between the TH and the control group with the Fisher's two-tailed exact test for categorical and with the Mann–Whitney test for continuous variables. Both tests were used for non-parametrical distributed data. Continuous variables were presented as the median, the 25th, and the 75th percentile. Categorical variables were presented as frequencies and percentages.

Variables that influenced the outcome with the p-value level of significance of $<$0.1 in the univariate analysis were included in the model for multivariate analysis along with TH. Hosmer–Lemeshow test was performed for a goodness of fit, and then the logistic regression analysis was conducted for the outcome variables: mortality and neurological disability. Odds ratio estimates were calculated with the 95% Wald confidence limits.