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Therapeutic hypothermia for severe adult herpes simplex virus encephalitis

ABSTRACT

Despite antiviral treatment and advances in critical care herpes simplex encephalitis (HSE) still has a poor outcome in a significant portion of patients. In severe cases of HSE reduced carbon dioxide reactivity is usually present and these patients don't respond to the usual treatment of brain edema and intracranial hypertension. We present case series of patients with severe form of HSE treated with therapeutic hypothermia (TH) and describe in detail the indications, methods and the rationale for its use.

In this case series patients presented with severely impaired consciousness and very high predicted death rate as measured by Glasgow coma scale and Acute Physiology and Chronic Health Evaluation (APACHE II) score respectively. According to our findings, TH in carefully selected patients with HSE holds promise as an adjunctive to the antiviral treatment.

INTRODUCTION

Despite antiviral treatment and advances in critical care herpes simplex encephalitis (HSE) still has poor outcome in 35% of patients, with mortality of 9% [1].

Antiviral treatment in HSE is well defined and consists of acyclovir in a dose of 30 mg/kg daily by intravenous route. However, during the early course of the disease treatment of intracranial hypertension (ICH) caused by brain edema with the possibility of brain herniation is of utmost importance for satisfactory outcome.

It has been proven that in patients with brain edema and reduced carbon dioxide reactivity (CO_2R) the usual treatment options such as administration of hyperosmolar solutions, hyperventilation, barbiturate induced coma and steroids are of humble efficacy or completely useless [2]. Furthermore, in traumatic brain injury and central nervous system infections reduction in CO_2R was a single most accurate predictor variable for poor outcome [2,3]. Consequently, in patients with HSE, reduced CO_2R and severe focal or diffuse brain edema the useful treatment option are still lacking while the death and brain herniation may ensue rapidly. Introduction of new treatment methods in such patients are desirable.

Of particular interest is therapeutic hypothermia (TH). It has well documented neuroprotective effects and may have a potential use in selected patients with inflammatory central nervous system (CNS) diseases [4,5,6,7].

In patients with transtentorial brain herniation life-saving decompressive craniectomy has been successfully employed. However, this surgical procedure has well documented adverse effects like meningitis and brain abscess. Furthermore, in these patients the cranioplasty is usually performed after six months and during that time the brain is not bone-protected while the patients are prone to seizures and thus to possible deleterious brain trauma. Cranioplasty alone is frought with complications such as epidural or subdural hematoma, wound healing disturbance, abscess, hygroma or cerebrospinal fluid fistula formation.

Single case of HSE treated with TH has been reported in the literature thus far [8]. We present case series of patients with severe form of HSE with reduced CO_2R. One patient had evident subfalcine and incipient transtentorial brain herniation TH. The indications, methods and the rationale for the use of the TH are described in detail.

CASE REPORTS

In the period between February 2009 and January 2011, 3 patients suffering from severe HSE had TH as an adjunctive treatment. All patients were mechanically ventilated, deeply sedated and relaxed using midazolam and vecuronium, respectively. The major indication for TH in these patients was reduced CO_2R and one patient had subfalcine and transtentorial brain herniation detected on computed tomography (CT) scan of the brain. The following treatment protocol was applied in all patients: mild hypothermia (32-34^{o} C) accompanied with daily assessment of cerebrovascular CO_2R , jugular bulb oximetry and optic nerve sheath diameter (ONSD). CT scan of the brain was indicated if worsening was detected on the TCD, jugular bulb oximetry and/or ONSD measurements in order to have timely neurosurgical consultation and decompressive craniectomy if indicated.

Transcranial Doppler ultrasound (TCD)

TCD measurement of CO_2R was performed by using a Multidop 4 X (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. The mean blood flow velocities (MBFV) were continuously recorded during normal ventilation and during interventions (induced hypercapnia, norepinephrine or urapidil infusion and hyperventilation). CO_2R was assessed using the breath-holding method (disconnection from the ventilator for 30 seconds in a deeply sedated and relaxed patient). BHI was calculated by dividing the percentage of MBFV increase during breath holding by the time (in seconds) of apnea.

Optic nerve sheath diameter (ONSD)

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. 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 correlates with a mean cerebrospinal fluid (CSF) pressure of more than 20 mmHg.

Jugular bulb oximetry

The jugular bulb catheter placement offers an opportunity for the measurement of SjO2 and calculation of lactate-oxygen index (LOI) using paired arterial and venous blood samples. The measurements were made twice daily during the period of hypothermia in order to detect desaturation of jugular bulb venous blood (SjO2 < 55%) or increased cerebral LOI > 0.08 (derived from arterio-jugular venous oxygen content difference and arterio-jugular venous lactate concentration difference) as reliable markers of cerebral hypoperfusion.

Therapeutic hypothermia

We used an internal protocol designed to achieve mild hypothermia (rectal temperature of 32-34^{o}C). Hypothermia was induced by intravenous infusion of cold (+4^{o}C - +8^{o}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 – 120 hours [9]. Duration of therapeutic hypothermia was determined by the recovery of CO_2R, improvement in LOI measurements and normalization of ONSD. This method of cooling was chosen because it allows stable temperatures during hypothermia as well as gradual rewarming. The patients were cooled at the fastest rate possible and rewarming rate was approximately 0.3 ^{o}C per hour. The blood flow rate was set to 150 ml/min, ultrafiltration rate (UFR) to zero ml/h and the replacement solution rate was set to 2000 ml/h. Enoxaparin was used for anticoagulation of the circuit. TH procedure underwent without side-effects occurring in all the patients.

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

In presented patients polymerase chain reaction detected herpes simplex 1 virus DNA in the cerebrospinal fluid. The patient with subfalcine and transtentorial brain herniation was to severely ill to be transferred to neurosurgery. One patient had an absent acustic window. Jugular bulb oximetry parameters remained stable during TH and LOI actually improved when target temperature was achieved. The ICU stay of

our patients ranged from 16-19 days and the outcome was favorable in all patients considering the severity of the disease [Glasgow Outcome Scale score (GOS) 4-5 and GCS 14-15]. Acute Physiology and Chronic Health Evaluation (APACHE II) score in our patients at admission predicted high mortality and GCS at admission revealed severely impaired consciousness. Demographic and clinical data of the patients are summarized in Table 1.

DISCUSSION

We present 3 patients with severe HSE and impaired CO_2R with presumable treatment failure of the standard treatment regimen for ICH that consists of hyperosmolar solutions, hyperventilation, and barbiturate induced coma. One patient with an absent acustic window had subfalcine and incipient transtentorial brain herniation detected on the CT scan of the brain. Urgent treatment options were required in order to avoid lethal outcome.

According to the literature as well as our own experience TH is highly effective in reducing intracranial pressure and has been used in one patient with similar presentation of HSE [4,5,6,7,8].

Our patients had severely impaired consciousness and very high predicted death rate as measured by GCS and APACHE II score respectively. However, despite the severity of illness all the patients had a good outcome after treatment with TH.

According to our, although limited experience, it seems prudent to employ TH in patients with severe HSE and reduced CO_2R. However, during TH patients should be carefully monitored and if any increment in intracranial pressure (ICP) is detected in comparison to the pre-TH ICP CT scan of the brain should be obtained and a neurosurgeon should be consulted. We used non-invasive ICP monitoring with ONSD and TCD as well as jugular bulb oximetry since neurosurgery is stationed outside our premises. Furthermore, in patients with severe HSE and evident brain herniation TH seems effective and is indicated if decompressive craniectomy cannot be performed for any reason.

Even though TH procedure requires experience it is available at the bedside, therapeutic temperature range can be achieved rather quickly and efficacy in this indication is favourable. Our protocol for TH as well as monitoring during the procedure is effective in temperature management, graduate rewarming and in detecting

complications, thus we can advocate its use in other centers as well. Of course, invasive ICP monitoring can be used as well with even more precision and compatible success.

Despite successful treatment intervention with TH in described patients, its use TH in this indication requires further investigation before definite conclusions can be drawn.

AUTHORS' CONTRIBUTION

All authors wrote, reviewed and revised the article and approved the final version of the manuscript. Dr. Marko Kutleša was primarily responsible for data collection and writing of the manuscript.

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Table 1. Demographic and clinical data of patients with herpes simplex encephalitis treated with hypothermia