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ABSTRACT

We present case series of adult community-acquired bacterial meningitis treated with hypothermia. The major criteria for therapeutic hypothermia (TH) was impaired carbon dioxide reactivity (CO_2R) assessed by Transcranial Doppler (TCD). In patients without temporal acoustic window, minor criteria (optic nerve sheath diameter ≥ 6.0 mm plus GCS ≤ 8) were required. According to our, although limited experience, the use of mild hypothermia in selected patients with community-acquired bacterial meningitis accompanied with appropriate monitoring could be a promising treatment tool.

INTRODUCTION

Despite recent advances in antibiotic therapy and critical care, bacterial meningitis continues to impose high rates of morbidity and mortality.[1-4] Given that bacterial meningitis freqently has associated poor outcomes, new treatment strategies are needed. Of particular interest is therapeutic hypothermia (TH). It has well documented neuroprotective effects and may have a potential use in selected patients with meningitis.[5,6] We present case series of adult community-acquired bacterial meningitis treated with hypothermia and describe in detail the methods and the rationale for its use.

PATIENTS AND METHODS

In the period between February 2009 and May 2010, ten patients suffering from severe community-acquired bacterial meningitis were treated with hypothermia. All patients were mechanically ventilated. The following treatment protocol was applied in all patients: mild hypothermia (32-34^{o} C) accompanied with daily assessment of cerebrovascular carbon dioxide reactivity (CO_2R) measured by Transcranial Doppler (TCD) and cerebral perfusion using the lactate-oxygen index (LOI) when available. The LOI was not measured in four patients because of difficult internal vein cannulation. Initial antimicrobial treatment consisted of ceftriaxone alone or in combination with ampicillin. Adjuvant steroid treatment was applied in seven patients.

Despite therapeutic hypothermia, two patients died within 48 hours from admission because of refractory intracranial hypertension. Two patients with severe residual neurological deficits (GOS 2) died after discharge from ICU because of late-onset nosocomial sepsis more than a month upon admission. In the surviving six patients, the ICU stay ranged from 8 to 36 (mean 22) days.

Of these survivors, two had severe and two had moderate residual neurological deficit, the most common being spastic hemiparesis and tetraparesis, respectively. One patient remained paraplegic with urinary incontinence due to severe pneumococcal myelitis. Two of the six survivors had a complete neurological recovery. The patients' demographic and clinical data are summarized in Tables 1-3.

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

Transcranial Doppler ultrasound (TCD)

TCD measurement of CO_2 reactivity (CO_2 R) 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 infusion and hyperventilation). CO_2 reactivity (CO_2 R) was assessed using the breath-holding method (disconnection from the ventilator for 30 seconds in a deep sedated and relaxed patient). The breath-holding index (BHI) was calculated by dividing the percentage of MBFV increase during breath holding by the time (in seconds) of apnea. The normal range of BHI is 1.03 – 1.65.[7]

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 mm correlated with a mean cerebrospinal fluid (CSF) pressure of 30 mmHg (elevated).[8,9]

Jugular bulb oximetry

The jugular bulb catheter placement offers an opportunity for the measurement of SjO_2 and calculation of lactate-oxygen index (LOI) using paired arterial and venous blood samples. The measurements were made daily during the period of hypothermia. Desaturation of jugular bulb venous blood (SjO_2 < 55%) with increased cerebral lactate-oxygen index (LOI > 0.08) [derived from

arterio-jugular venous oxygen content difference ($AjVDO_2$) and arterio-jugular venous lactate concentration difference (AVDL)] are reliable markers of cerebral hypoperfusion.[10,11] Furthermore, increased SjO_2 (>75%) and LOI with decreased $AjVDO_2$ could be ominous signs of extreme intracranial hypertension and commonly represent a preterminal event.[10,11]

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 – 96 hours. 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.

DISCUSSION

While hypothermia has already been used for neuroprotection in a variety of neurological and non-neurological conditions, this method has been exceptionally applied to the treatment of central nervous system infections.[5,6,13-16] Other adjunctive treatment options, such as the use of corticosteroids, despite their beneficial effects in majority of patients have not substantially changed disease outcomes among patients with most severe pneumococcal meningitis.[17]

Common neurological sequelae in survivors of bacterial meningitis may result from neuronal damage, ischemic encephalopathy or ischemic stroke. In our opinion, current therapies do not adequately address the underlying pathophysiology leading to neurologic damage associated with bacterial meningitis. Current treatments are frequently aimed at reducing intracranial pressure and depend on cerebral vasoreactivity.[18,19] In severe bacterial meningitis, however, cerebral blood flow (CBF) autoregulation is often damaged. Furthermore, cerebral metabolic oxygen demand ($CMRO_2$) and CBF coupling is frequently disrupted and leads to multisegmental hypoperfusion or hyperemia. The use of mannitol in patients with impaired cerebral arterioles carbon dioxide reactivity (CO_2R) carries the risk for paradoxical aggravation of brain edema because of possible mannitol leakage into the brain tissue . Therefore, the administration of mannitol should be discouraged in such patients. In

addition, the appropriate monitoring of cerebral perfusion pressure (CPP), intracranial pressure (ICP), cerebral oxygen demand, consumption and extraction in these patients is necessary.

The effects of mild hypothermia may target the pathophysiological mechanisms that are in effect during bacterial meningitis because most of them are temperature dependent.[20,21]

Hypothermia results in neuroprotection through a variety of mechanisms. Decreased body temperature causes reduced production of reactive oxygen and nitrogen species, inhibition of the neuroexcitatory cascade, a reduction in proinflammatory cytokine level, maintenance of blood-brain barrier integrity, decreased intracranial pressure, and finally decreased neuronal apoptosis.[22-28] Additionally, adverse events are noted to be rare. When those events occur, they are typically minor.[5]

According to our framework, the selection of patients for induced hypothermia is primarily based on cerebral arterioles CO_2 reactivity. The criteria for therapeutic hypothermia are GCS ≤ 8 accompanied with optic nerve sheath diameter (ONSD) > 6.0 mm if the temporal acoustic window is absent and cerebral vasoreactivity cannot be assessed.

Because of strong correlation of BHI with the severity (particularly with GCS score) and the outcome of the disease, we defined the BHI level of ≤ 0.86 as inclusion criteria for hypothermia. Chemoregulation in our patients was severely impaired or completely absent.

We believe that marked reduction of CO_2 reactivity, measured by TCD, accompanied with increased ONSD and altered mental status (GCS ≤ 8) reliably select patients who are candidates for urgent hypothermia induction. In patients with preserved CO_2 reactivity, the use of hypothermia probably would not yield additional benefit when compared to the standard treatment regimen. The mortality rate in patients with bacterial meningitis and preserved vasoreactivity treated with standard regimen regardless of disease severity was zero (0/14) compared with 25% (5/20) in patients with impaired vasoreactivity (unpublished data).

In all patients with jugular bulb catheter the measurements showed cerebral perfusion impairment (increased LOI) (Table 3). Vasopressors were used to support cerebral perfusion pressure (CPP). Low doses of norepinephrine infusion in addition to hypothermia were sufficient to significantly improve the MBFV and LOI without significant systemic hypertension. A marked reduction in ONSD during hypothermia was also noted (Table 3).

With respect to disease severity, the outcome of our patients was generally satisfactory (Table 1). If the standard treatment regimen had been applied the disease would likely

have been fatal. At admission, one patient had TCD signs of cerebral circulatory arrest while the others were elderly and had severe global cerebral hypoperfusion. The mortality rate in such patients reaches 69%.[3]

While lowering of body temperature may take several hours in pyretic patients, CVVHF allows the maintenance of a stable body temperature. Our patients had no significant variations in body temperature. In addition, the use of CVVHF allows gradual rewarming of the patient upon recovery.

While there is evidence from animal studies that hypothermia may be beneficial in meningitis and while scarce clinical experience suggests a role for hypothermia, large scale randomized clinical trials are needed.[27,28] Inclusion criteria in these trials should be based primarily on the cerebral vasoreactivity status and not on pure randomisation and clinical impression. The use of hypothermia during meningitis is complex, but it likely has a physiologic role in treating bacterial meningitis. It may assist with the reduction in cerebral metabolism, cerebral blood volume (CBV), lowering of the intracranial pressure and suppression of the inflammatory host response allowing maintainance of sufficient cerebral perfusion pressure. Adequate and complete treatment balancing antimicrobial treatment, deep sedation, and controlled cerebral perfusion pressure early in the course of disease is critical. The recovery of CO_2 reactivity cannot be expected before the fourth day of treatment according to our experience. Therefore, we recommended the use of hypothermia (if indicated) as soon as possible and at least during the first three days after presentation.

Despite numerous favorable effects of hypothermia, a more comprehensive approach should be employed. It may be taken into account as an adjunctive therapy that has a role alongside established treatments. According to our findings, hypothermia in carefully selected patients holds promise.

AUTHORS' CONTRIBUTION

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

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REFERENCES

1. Lu CH, Huang CR, Chang WN, Chang CJ, Cheng BC, Lee PY, et al. Community-acquired bacterial meningitis in adults:the epidemiology, timing of appropriate antimicrobial therapy, and prognostic factors. Clin Neurol Neurosurg 2002; 104(4):352-358.

2. Cohen J. Management of bacterial meningitis in adults:Algorithm from the British Infection Society represents current standard of care. Br Med J 2003; 326(7397):996-997.

3. Lepur D, Baršić B. Community-acquired bacterial meningitis in adults: antibiotic timing in disease course and outcome. Infection 2007; 35(4):225-231.

4. Van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. N Engl J Med 2006; 354:44-53.

5. Marion D, Bullock MR. Current and future role of therapeutic hypothermia. J Neurotrauma 2009; 26(3):455-467.

6. Varon J, Acosta P. Therapeutic hypothermia-past, present and future. Chest 2008; 133:1267-1274.

7. Zavoreo I, Demarin V. Breath holding index in the evaluation of cerebral vasoreactivity. Acta Clin Croatica 2004; 43:15-19.

8. Hansen HC, Helmke K. Validation of the optic nerve sheath response to changing cerebrospinal fluid pressure: ultrasound findings during intrathecal infusion tests. J Neurosurg 1997; 87:34-40.

9. Lindbloom P. Measuring the optic nerve sheath diameter in a head-injured man. JAAPA 2008; 21(12):27-28.

10. Robertson CS, Narayan RK, Gokaslan ZL, Pahwa R, Grossman RG, Caram P Jr, et al. Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. J Neurosurg 1989; 70:222-230.

11.Valadka AB, Furuya Y,Hlatky R, Robertson CS. Global and regional techniques for monitoring cerebral oxidative metabolism after severe traumatic brain injury. Neurosurg Focus 2000; 9(5):1-3.

12. Kastenbauer S, Winkler F, Fesl G, Schiel X, Ostermann H, Yousry TA, et al. Acute severe spinal cord dysfunction in bacterial meningitis in adults:MRI findings suggest extensive myelitis. Arch Neurol 2001; 58:806-810.

13. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353(15):1574-1584.

14. Robinson A, Buckler JMH. Emergency hypothermia in meningococcal meningitis. Lancet 1965;1(7376): 81-88.

15. Veghelyi PV. Emergency hypothermia in meningococcal meningitis. Lancet 1965; 1(7387):710.

16. Cuthbertson BH, Dickson R, Mackenzie A. Intracranial pressure measurement, induced hypothermia and barbiturate coma in meningitis associated with intractable raised intracranial pressure. Anaesthesia 2004; 59:908-911.

17. de Gans**,** J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347(20):1549-1556.

18. Messeter K, Nordstrom CH, Sundbarg G, Algotsson L, Ryding E. Cerebral hemodynamics in patients with acute severe head trauma. J Neurosurg 1986; 64:231-237.

19. Schalen W, Messeter K, Nordstrom CH. Complications and side effects during thiopentone therapy in patients with severe head injuries. Acta Anaesthesiol Scand 1992;36:369-377.

20. Polderman KH. Mechanism of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37(7) Suppl:186-202.

21. Koedel U, Scheld WM, Pfister HW. Pathogenesis and pathophysiology of pneumococcal meningitis. Lancet Infect Dis 2002; 2(12):721-736.

22. Aibiki M, Maekawa S, Ogura S, Kinoshita Y, Kawai N, Yokono S. Effect of moderate hypothermia on systemic and internal jugular plasma IL-6 levels after traumatic brain injury in humans. J Neurotrauma 1999;16(3):225-232.

23. Kimura A, Sakurada S, Ohkuni H, Todome Y, Kurata K. Moderate hypothermia delays proinflammatory cytokine production of human peripheral blood mononuclear cells. Crit Care Med 2002;30(7):1499-1502.

24. Winfree CJ, Baker CJ, Connolly ES Jr, Fiore AJ, Solomon RA. Mild hypothermia reduces penumbral glutamate levels in the rat permanent focal cerebral ischemia model. Neurosurgery 1996; 38(6):1216-1222.

25. Busto R, Globus MY, Dietrich WD, Martinez E, Valdés I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. Stroke 1989; 20(7):904-910.

26. Xu L, Yenari MA, Steinberg GK, Giffard RG. Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade. J Cereb Blood Flow Metab 2002; 22(1):21-28.

27. Irazuzta JE, Pretzlaff RK, Zingarelli B, Xue V, Zemlan F. Modulation of nuclear factor-kappaB activation and decreased markers of neurological injury associated with hypothermic therapy in experimental bacterial meningitis.Crit Care Med 2002; 30(11):2553-2559.

28. Irazuzta JE, Pretzlaff R, Rowin M, Milam K, Zemlan FP, Zingarelli B. Hypothermia as an adjunctive treatment for severe bacterial meningitis. Brain Res 2000; 881(1):88-97.

TABLES

Table 1. Demographic and clinical data of patients with community-acquired bacterial meningitis treated with hypothermia - Part one

Patient No.	Age/sex	Day of disease*	Coexisting conditions	Seizures	Etiology	APACHE II	GCS at admission	GCS at discharge from ICU	GOS[1]	Karnofsky score (%)[2]
1	82/F	1	Otitis	Yes	*S. pneumoniae (PSSP†)*	31	8	15	4	50
2	63/M	3	Otitis	No	*S. pneumoniae* (PRSP‡)	22	4	15	3**	60
3	47/F	2	Immunocompromised***	No	*S. pneumoniae (PSSP)*	23	6	15	5	90
4	71/F	2	Rectal adenocarcinoma	No	*S. pneumoniae (PSSP)*	32	7	14	4	50
5	76/M	1	Otitis	No	*S. pneumoniae (PSSP)*	24	9	NA	2	NA
6	78/F	2	Immunocompromised	Yes	*S. pneumoniae (PSSP)*	33	3	NA	2	NA
7	61/F	1	Acute renal failure	No	*E. coli*	33	3	NA	1	NA
8	68/F	2	Immunocompromised, Pneumonia	No	*S. pneumoniae (PSSP)*	34	3	NA	1	NA
9	70/M	1	Immunocompromised	No	*S. pneumoniae (PSSP)*	26	8	15	5	90
10	75/F	1	Immunocompromised	No	*S. pneumoniae (PSSP)*	33	4	14	3	40

Legend:

* day of disease on which hypothermia was started
** paraplegia caused by severe myelitis
***Immunocompromised - the use of immunosuppressive drugs or the presence of diabetes mellitus, chronic renal failure or alcoholism

Table 2. Demographic and clinical data of patients with community-acquired bacterial meningitis treated with hypothermia - Part two

Patient No.	CSF cell count[3] (cells/ mm^3)	CSF- blood glucose ratio[4]	CSF protein concentration (mg/L)[5]	CSF lactate concentration (mmol/L)[6]	BHI_m[7]	Vasopressor support	Adjuvant dexamethasone treatment	Duration of hypothermia (hours)	Meningitis -related complications	Hypothermia/CVVHF -related complications
1	36 000	0,0	7 450	18,0	N/A	Yes	Yes	72	none	none
2	200 000	0,0	12 100	15,9	0,876	Yes	Yes	72	severe myelitis	none
3	9 216	0,47	1 843	8,6	0,610	No	No	72	none	none
4	2 560	0,0	9 447	20,4	0,644	No	Yes	72	none	none
5	1 160	0,03	11 936	25,9	0,350	No	Yes	72	refractory brain edema	none
6	1 633	0,03	1 790	25,4	0,090	Yes	Yes	96	ischemic stroke	none
7	12 997	0,39	7 348	18,7	0,210	Yes	Yes	48	refractory brain edema	none
8	19 200	0,02	7 273	-	0,342	Yes	Yes	48	ventriculitis, refractory brain edema	none
9	4 437	0,23	8 533	19,3	0,495	No	No	96	none	moderate amylase increase
10	4 266	0,0	6 031	12,4	0,0	Yes	No	96	ischemic leukoencephalopathy	none

Legend:

[1] Score on Glasgow Outcome Scale - at discharge from ICU [1(death), 2(vegetative state), 3(severe disability), 4(moderate disability), 5(mild or no disability)]
[2] Karnofsky performance score - at discharge from ICU
[3] CSF white cell count (normal value: < 5 cells/mm^3)
[4] CSF-blood glucose ratio (normal value: > 0,4)
[5] CSF protein concentration (normal range: 150-450 mg/L)
[6] CSF lactate concentration (normal range: 1,58-2,03 mmol/L)
[7] Mean breath-holding index - at admission to ICU

† PSSP = penicillin-susceptible *Streptococcus pneumoniae*
‡ PRSP = penicillin-resistant *Streptococcus pneumoniae*

Table 3. The brain edema and cerebral perfusion indicators before and during therapeutical hypothermia

Patient No.	Duration of hypothermia (hours)																			
	0					24					48					72				
	BHI_m [1]	ONSD-Right [2]	ONSD-Left	LOI [3]		BHI_m	ONSD-Right	ONSD-Left	LOI		BHI_m	ONSD-Right	ONSD-Left	LOI		BHI_m	ONSD-Right	ONSD-Left	LOI	
1	-	6,6	6,8	0,153		-	3,7	4,9	0,034		-	3,5	5,0	0,009		-	-	-	0,01	
2	0,876	6,6	6,6	-		0,850	6,0	6,0	-		0,910	5,6	5,7	-		1,000	4,7	5,0	-	
3	0,610	7,4	6,8	0,060		0,584	6,3	5,9	0,029		0,385	5,9	5,9	0,018		0,875	4,8	5,0	0,019	
4	0,644	6,4	6,0	0,440		0,650	6,0	5,6	0,007		0,580	5,6	5,0	0,002		0,780	5,0	4,5	0,021	
5	0,350	6,6	6,5	-		0,420	6,3	6,1	-		0,382	5,5	5,6	-		0,413	-	-	-	-
6	0,090	7,1	7,4	-		0,00	6,3	7,4	-		0,272	7,1	6,9	-		-	-	-	-	
7	0,210	6,2	6,8	-		0,838	5,7	5,8	-		0,230	5,8	6,0	-		-	-	-	-	
8	0,342	6,4	6,0	0,114		0,410	6,2	5,9	0,080		0,450	6,3	5,9	0,090		-	-	-	-	
9	0,495	7,6	7,4	0,036		0,060	6,8	6,4	0,060		0,380	5,9	5,5	0,033		0,550	-	-	0,010	
10	0,0	6,1	6,0	0,074		0,0	5,8	5,5	0,078		0,744	5,6	5,3	0,060		0,710	-	-	0,040	

Legend:

[1] BHI_m = mean breath holding index (normal range: 1,03 – 1,65)

[2] ONSD = optic nerve sheath diameter (normal value < 5,0 mm)

[3] LOI = lactate-oxygen index (normal value < 0,03)