The Lund Concept in 1999

Carl-Henrik Nordström, M.D., Ph.D.
Department of Neurosurgery
Lund University Hospital
S-221 85 Lund
Sweden

A new therapeutic approach to reduce increased ICP, denoted the "Lund therapy" of a severe head injury, was introduced a few years ago together with the first clinical outcome results [1]. The Lund therapy is based on physiological principles for cerebral tissue and blood volume regulation and allows for both the risks of raised ICP and the risks of compromised microcirculation. The therapy thus aims at preventing cerebral hypoxia simultaneously with taking measures that counteract transcapillary filtration. In summary, our treatment protocol includes preservation of a normal colloidal absorbing force, a reduction of intracapillary pressure through reduction of systemic blood pressure by antihypertensive therapy (a b_1-antagonist, metoprolol, combined with an a_2-agonist, clonidine) and a simultaneous, moderate constriction of precapillary resistance vessels with low-dose thiopental and dihydroergotamine. Dihydroergotamine is known to preferentially constrict the large venous vessels [2,3] and it will reduce intracranial blood volume mainly through this mechanism. Clonidine in combination with the thiopental and other sedatives and analgesics simultaneously reduces the high level stress response and the endogenous catecholamine release, in turn improving microcirculation of the brain as well as of other tissues of the body. Optimum general intensive care regarding fluid therapy to keep normovolaemia (to optimise cerebral microcirculation), regarding lung function, nutrition, electrolytes etc, is carefully effectuated.

In this presentation I will first briefly review the pharmacological principles of the Lund concept. A short presentation of the clinical outcome data, previously presented in detail [4], will be given. Our data show that clinical outcome in this group of patients is considerably improved compared with a previously published patient material with the same entry criteria but treated according to conventional intensive care principles including high dose thiopental, hyperventilation and preservation of a high cerebral perfusion pressure [5]. Finally I will briefly discuss new experiences obtained from intracerebral microdialysis with bedside biochemical analysis during these circumstances.

Pharmacological principles of the Lund concept

Reduction of capillary hydrostatic pressure

Mean arterial blood pressure is reduced to the physiological level for the age of the individual patient with a combination of the b_1-antagonist metoprolol (0.2-0.3 $mg \cdot kg^{-1} \cdot 24h^{-1}$ *i.v.*) and the a_2-agonist clonidine (0.4-0.8 $\mu g \cdot kg^{-1}$ x 4-6 *i.v.*) [1,6]. The antihypertensive treatment is initiated when the patients are clearly normovolaemic as obtained by red cell and albumin/plasma transfusions to normal albumin and haemoglobin values and to a normal central venous pressure. A CPP of 60-70 mm Hg

is usually considered optimal but if necessary to control ICP, a CPP of 50-mm Hg for adults and 40 mm Hg for children are accepted. Dihydroergotamine is given with the purpose of decreasing cerebral blood volume mainly via constriction of venous vessels. Like thiopental, dihydroergotamine also has a precapillary vasoconstrictor effect, which will contribute to lowering the intracapillary hydrostatic pressure [3,7,8].

Reduction of cerebral blood volume

Intracranial blood volume is reduced both on the arterial side with thiopental [9] and dihydroergotamine [3,7,8] and on the venous side with dihydroergotamine [2,3]. Dihydroergotamine is always given at the lowest doses necessary to reduce intracranial pressure to values below 20-25 mm Hg. Dihydroergotamine is not given for more than five days to minimise the risks of compromising peripheral circulation, in particular in patients with fractures of the extremities or renal insufficiency. The maximum doses of dihydroergotamine are: 0.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ day one, 0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ day two, 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ day three, 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ day four, and 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ day five. In most patients intracranial pressure can be controlled at values below 20-25 mmHg with lower doses and a faster discontinuation of dihydroergotamine than five days.

Reduction of stress response and cerebral energy metabolism

Stress response is reduced by liberal use of sedatives (benzodiazepines) and analgesics (opioids). A further reduction of the stress response and catecholamine release is obtained by a continuous infusion of low-dose thiopental (0.5-3 $mg \cdot kg^{-1} \cdot h^{-1}$) and fentanyl (2-5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) but also by treatment with the b_1-antagonist metoprolol and the a_2-agonist clonidine (see above). The dose of thiopental was low to avoid cardiac inhibition, pulmonary complications and other side effects [10].

Fluid balance and maintenance of colloid osmotic pressure

A balanced or moderately negative fluid balance is a part of the treatment protocol for the purpose of reducing cerebral interstitial space. It is achieved by diuretics (furosemide) and albumin infusion. Red cell transfusions and albumin are given to achieve normal values (Hb/s 125-140 g/l, alb/s ~40 g/l) to ensure normovolaemia and to optimise oxygen supply. The albumin/plasma/blood transfusions also serve the purpose of attaining a normal colloid osmotic pressure favouring transcapillary absorption. All patients are given a low calorie enteral nutrition (max energy supply 15-20 $kcal \cdot kg^{-1} \cdot 24\ h^{-1}$).

Drainage of cerebrospinal fluid

The ventricular catheter, inserted in all patients for the purpose of ICP recording, can be used for drainage of cerebrospinal fluid. Except for halting an acute life-threatening increase in intracranial pressure, cerebrospinal fluid drainage is not, however, used continuously in the acute phase due to the risk of ventricular collapse.

Clinical results
Clinical material

The presentation includes only those head injured patients (15-20%) who developed a dangerous increase in ICP (>25 mm Hg) despite surgical evacuation of focal mass lesions, adequate sedation, controlled ventilation, and

good general intensive care. During the period February 1982 to March 1986, 38 patients were managed according to the principles for brain oedema in use at that time (and similar to the therapy accepted in most neurotrauma centres today). The main therapy to reduce ICP in these patients was controlled hyperventilation and high-dose thiopental in combination with preservation of a high cerebral perfusion pressure.

This group of patients, the outcome data of which have been presented previously (5,10), is used as a reference material for the present summary of the "Lund Concept" which includes 53 patients treated from January 1989 to January 1994. The principles of this treatment were briefly summarised above.

Age groups	Good recovery Moderate disability		Severe disability Vegetative state		Dead		Total	
years	**1982-86**	**1989-94**	**1982-86**	**1989-94**	**1982-86**	**1989-94**	**1982-86**	**1989-94**
<21	8	20	0	2	12	1	20	23
21-40	6	15	1	3	5	2	12	20
41-60	2	6	3	2	1	1	6	9
>60	0	1	0	0	0	0	0	1
Sum	16	42	4	7	18	4	38	53
(Per cent)	(42)	(79)	(11)	(13)	(47)	(8)		

Diagnostic groups	Good recovery Moderate disability		Severe disability Vegetative state		Dead		Total	
	1982-86	**1989-94**	**1982-86**	**1989-94**	**1982-86**	**1989-94**	**1982-86**	**1989-94**
Epidural	1	1	1	0	0	0	2	1
Subdural	1	5	0	1	2	0	3	6
Intracerebral	6	17	3	5	6	2	15	24
No mass	8	19	0	1	10	2	18	22
Sum	16	42	4	7	18	4	38	53
(Per cent)	(42)	(79)	(11)	(13)	(47)	(8)		

Table 1: **Outcome according to Glasgow Outcome Scale.**

Clinical outcome

Table 1 shows outcome separately in four age groups and four diagnostic groups (data from [4]). Cases denoted epidural or subdural hematoma had pure hematoma of the respective category needing surgical evacuation. Intracerebral lesions include focal cerebral contusions and/or intracerebral hematoma evacuated surgically. In some cases these lesions were combined with an extracerebral hematoma (usually a subdural hematoma). The group "no mass" includes all patients who were not treated with surgical evacuation of focal mass lesions. In the historical control group of 38 patients (1982-86) 18 patients died, two remained in a vegetative state, two were severely disabled, and 16 had a favourable outcome [5]. Mortality was significantly lower in the group treated according to the new protocol than in the group treated according to conventional principles ($p < 0.0001$) and the ratio of patients with outcome denoted vegetative or severe disability was about the same. The ratio of patients with a favourable outcome (good recovery/moderate disability) thus was significantly higher in the group treated according to the new protocol ($p < 0.001$).

All patients and their relatives have also been subjected to later follow up studies including structured interviews to evaluate the long-term outcome and the quality of life [11].

Intracerebral microdialysis with bedside biochemical analysis

We have used intracerebral microdialysis as a routine in all patients with severe traumatic brain injuries since more than three years ago. In patients with focal cerebral lesions one microdialysis catheter has been positioned in the "best" hemisphere, usually in the cerebral cortex via a separate burr hole about one cm in front of the ICP recording device. One or two catheters have been positioned in the "worst" position i.e. into the cortical "penumbra" zone after evacuation of a hematoma or focal brain contusion. One of the objectives for these measurements has been to evaluate the biochemical effects of the reduction in MAP (see above).

Biochemical analyses have been effected at the bedside with the CMA 600. Presently, the CMA 600 can analyse glucose, pyruvate, lactate, glycerol, glutamate, and urea with enzymatic micro techniques. These variables may give information regarding various aspects of regional metabolism: substrate availability (glucose), redox state (lactate/pyruvate ratio), degradation of glycerophospholipids in the cell membranes (glycerol), liberation of excitatory amino acids (glutamate), and, possibly, regional blood flow and/or the state of the blood brain barrier (urea). We have recently summarised our data regarding normal values of human brain [12] and cerebral biochemistry in fatal brain injuries [13,14].

The biochemical effect of treatment according to the Lund Concept is illustrated in one patient in figure 1. This 23-year old man was operated with evacuation of a temporal contusion. Shortly after surgery ICP returned to 20 mm Hg or above although the bone flap (fractured into multiple fragments) had been removed. Treatment according to the "Lund Concept" was started. ICP remained essentially unchanged during the first 24 hours but later gradually decreased to a normal level. During these 24 hours average MAP was 73 mm Hg (maximum 83, minimum 63 mm Hg) and average CPP was 54 mm Hg (maximum 68, minimum 39 mm Hg). The "Lund therapy" was continued and we accepted this low CPP since the pattern of the energy metabolites in the penumbra zone surrounding the evacuated focal contusion showed a continuous normalisation. Presently, we have similar experiences from about 50 patients.

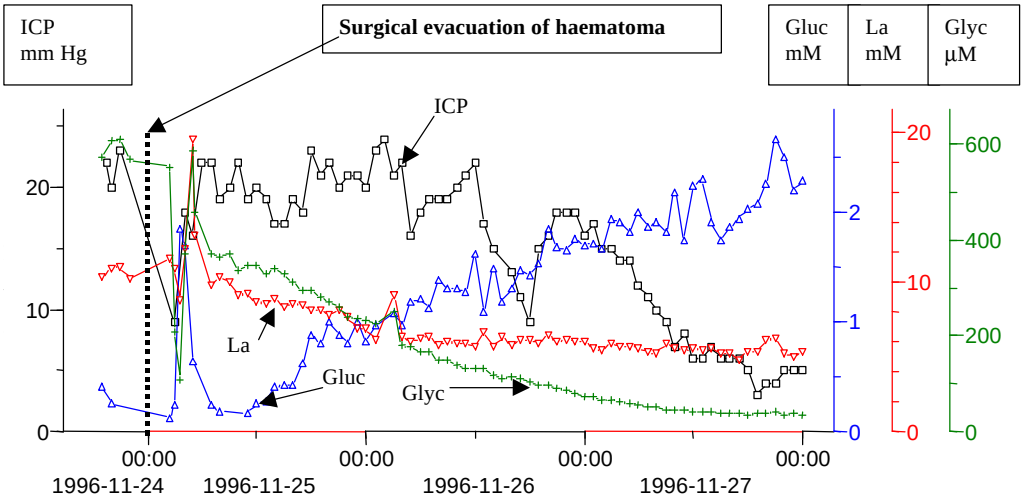

Figure 1. ICP and cerebral interstitial concentrations of lactate (La), glucose (Glu), and glycerol (Gly) in the penumbra zone after evacuation of a focal temporal contusion. The figure illustrates a normalisation of cerebral energy metabolism in spite of a remaining high ICP and a pharmacological reduction of CPP.

The "Lund Concept" is supposed to be most effective if the BBB is disrupted. There is presently no technique available for bedside evaluation of the permeability of the BBB. The microdialysis technique may offer a possibility for such measurements. We have recently finished a preliminary experimental and clinical study, which indicates that urea (which can be analysed bedside with the CMA 600), might be used as tracer for such measurements [15]. In summary, treatment of increased ICP post trauma according to the "Lund Concept" is supported in a relatively large number of experimental studies (for references see [1,3,4,8]). The clinical outcome results are excellent [4] as briefly summarised above. Finally, our experiences from intracerebral microdialysis with bedside biochemical analysis support the principles behind the "Lund therapy". Intracerebral microdialysis is presently an important technique for the supervision of patients with severe traumatic brain lesions and is used as guidance for the choice of therapy.

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Address for correspondence:
Dr. Med. C. H. Nordström
Department of Neurosurgery
University Hospital
221 85 Lund. Sweden