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Severe Traumatic Brain Injury Management and Clinical Outcome Using the Lund Concept

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Running title: The Lund concept: management and outcome

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Highlights

The Lund Concept to treat a severe traumatic head injury was introduced in 1992

The Lund Concept is based on principles for brain volume and brain perfusion regulation

Components in the Lund Concept find support in experimental and clinical studies

Several small outcome studies give support for the Lund concept.

Like other guidelines, the Lund Concept is not tested in a large randomised study

Abstract

This review covers the main principles of the Lund concept for treatment of severe traumatic brain injury. This is followed by a description of results from clinical studies in which this therapy or a modified version of the therapy has been used. Unlike other guidelines, which are based on meta-analytical approaches, important components of the Lund concept are based on physiological mechanisms for regulation of brain volume and brain perfusion and to reduce transcapillary plasma leakage and the need for plasma volume expanders. There have been 8 non-randomised and 2 randomised outcome studies with the Lund concept or modified versions of the concept. The non-randomised studies indicated that the Lund concept is beneficial for outcome. The 2 randomised studies were small but showed better outcome in the groups of patients treated according to the modified principles of the Lund concept than in the groups given a more conventional treatment.

Introduction

Originally, the Lund concept (LC) for treatment of severe traumatic brain injury (sTBI) was a theoretical approach mainly based on the physiological and pathophysiological principles of brain volume and brain perfusion regulation (Asgeirsson et al., 1994; Grände et al.; 1997; Grände, 2006). The concept aimed at counteracting an increase in intracranial pressure (ICP) or to reduce an already raised ICP after sTBI, while improving compromised perfusion in and around the contusion areas at the same time. It can be described as an ICP- and perfusion-guided approach. The main components of the LC have found support in experimental and clinical studies, as described later in this review.

So far, no TBI guidelines have been tested in a large randomized clinical trial and from that point of view there is limited high-level clinical evidence for all TBI guidelines presented today (Muzevic and Splavski, 2013). A specific therapy therefore must be based on other types of input such as smaller clinical outcome studies including metaanalysis, experimental studies and basal physiological principles.

Even though different guidelines differ in essential aspects, the Brain Trauma Foundation's guidelines have moved closer to the LC during the past 10 years, e.g. concerning cerebral perfusion pressure (CPP) and the use of vasopressors (Bullock et al., 1996; Bullock et al., 2000; Brain Trauma

Foundation, 2007). In contrast to Brain Trauma Foundation guidelines—in which the ICP-reducing therapy should start when ICP is above 20 mmHg (Brain Trauma Foundation, 2007)—the LC recommends that the therapy should start as early as possible after arrival at the hospital, in an attempt to counteract the development of brain oedema and to ensure that there is early optimization of the perfusion. To our knowledge, no clear side effects have appeared with the LC, which means that it can be given early and to all patients independent of severity of the injury and independent of the degree of autoregulation. The LC has not changed since its introduction, except that dihydroergotamin is no longer used. Dihydroergotamin, which reduces ICP via cerebral venous constriction, was used in the initial version of the concept in patients with uncontrolled increase in ICP (Asgeirsson et al., 1994). It was withdrawn because of possible side effects related to peripheral vasoconstriction in high doses. For details of the LC guidelines, see; Asgeirsson et al. (1994) Grände (2006), Grände (2011), Olivecrona et al. (2007), and Olivecrona et al. (2009). **A simplified schematic algorithm of the LC used in the clinical setting is shown in Figure 1.**

Measurement of intracranial pressure and cerebral perfusion pressure

Like in other guidelines, monitoring of ICP is an essential part of the LC, and the monitoring should be started as soon as possible after the arrival to the hospital. The method of ICP monitoring can either be by external ventricular drainage or by an intraparenchymal device. It is also crucial to

monitor the arterial pressure and the mean arterial pressure (MAP).

The reference points for MAP and ICP must be identical when calculating CPP. For example, a head elevation of 15 degrees with the zero-reference point for the ICP at the external meatus and the zero-reference point for the MAP at the heart level gives a difference of around 10 mmHg compared to treatment of the patient without head elevation. This difference must be compensated for in the calculation of CPP.

Treatment of ICP

Early surgical evacuation of available intracranial mass lesions such as haematomas and focal lesions (sometimes in combination with craniotomy, see below) is recommended to decrease ICP and to reduce other potential adverse effects of the lesions (Gudeman et al., 1982; Hartings et al., 2014).

When CPP is high after the trauma (Simard and Bellefleur, 1989) or increased with vasopressors, there is a risk that the pressure-induced better perfusion and oxygenation will be transient in the injured brain with capillaries passively permeable to small solutes, as the high CPP will induce increase in hydrostatic capillary pressure with transcapillary filtration and aggravate the vasogenic brain oedema (Trevisani et al., 1994; Kongstad and Grände, 2001; Oertel et al., 2002). Vasoconstrictors may also have extracranial side effects, such as acute respiratory distress syndrome

(ARDS) (Robertson et al., 1999; Contant et al., 2001), and they may cause increased general leakage of plasma, resulting in hypovolemia and general tissue oedema (Dubniks et al., 2007; Nygren et al., 2010). This type of side effect can be reduced by accepting a lower CPP than the initially recommended lowest CPP of 70 mmHg (Bullock et al., 1996; Bullock et al., 2000), and by avoiding or limiting the use of vasopressors. LC therefore advocates the use of anti-hypertensive treatment (beta-1 blockade, alpha-2 agonists, angiotensin II antagonist) (Asgeirsson et al., 1994, 1995, Grände, 2006). It has been shown that beta-blockade in sTBI patients is independently associated with improved survival (Cotton et al., 2007; Inaba et al., 2008) and that alpha-2 agonist effectively reduces blood pressure in sTBI patients (Kariya et al., 1999) and is neuroprotective in an in vitro model for traumatic brain injury (Schoeler et al., 2012). Beta-blockade has also a documented protective effect on the cardiovascular system after a sTBI (Cruickshank et al., 1987). **Angiotensin II antagonist may also be beneficial by counteracting the proinflammatory effects of angiotensin (Ruiz-Ortega et al., 2001). It may also be beneficial to avoid noradrenaline-induced proinflammatory effects (Miksa et al., 2005).**

If CPP is high in spite of the anti-hypertensive therapy, it can be reduced by moderate head elevation in cardiovascular stable patients. Head elevation will lower hydrostatic capillary pressure in the brain, resulting in a slow reduction in ICP, but it may also cause a fast decrease in ICP by passive reduction in intracranial blood volume. This reduction in blood volume occurs mainly on the arterial side as the brain is protected from venous

pressure variations by a variable passive venous outflow resistance (Wolf and Forbes, 1928; Kongstad and Grände, 1999). Extensive head elevation (> 15 - 20°) should be avoided as it may reduce venous return to the heart, especially in unconscious and sedated patients with depressed baroreceptor reflex response (Ketch et al., 2002).

CPP normally stays in the range of 60–70 mmHg in adult patients treated according to the LC (Ståhl et al., 2001; Naredi et al., 2001; Grände, 2006; Grände 2011; Olivecrona et al., 2007; Olivecrona et al., 2009). If necessary to control ICP, a minimum CPP of 50 mmHg has been accepted in adults and 40 mmHg in small children after an individual evaluation, **but only if the patient is treated towards normovolemia** with the fluid therapy advocated in the LC. Nowadays, these CPP values are also recommended in the US Guidelines for adults and children (Brain Trauma Foundation, 2007; Brain Trauma Foundation Pediatric, 2010). A microdialysis study on adult patients with severe traumatic brain lesions has shown that CPP may be reduced to 50 mmHg without disturbance of oxygenation, provided the physiological, the pharmacological and the fluid principles of the LC are recognized (Nordström et al., 2003).

Except that it helps to maintain normovolemia, normalisation of plasma oncotic pressure with albumin as plasma volume expander may also counteract filtration in the injured brain according to the classical Starling fluid equilibrium equation. The beneficial absorbing effects of albumin,

however, may have been somewhat overestimated. Firstly, at increased permeability after the trauma in the whole body, more plasma fluid and proteins will leak to the interstitium and the effectiveness of albumin as plasma volume expander will be reduced. Secondly, a revision of the classical Starling principles incorporating the endothelial glycocalyx layer means a reduced absorption effect of the transcapillary oncotic pressure in favour of the hydrostatic capillary pressure (Woodcock and Woodcock, 2012). This hypothesis, however, is highly controversial and has still not been confirmed (Rippe, 2008). Finally, a randomised post hoc study (the SAFE-TBI study, see below) has shown better outcome with saline than with albumin as plasma volume expander to sTBI patients. Thus, while saline can be criticised as plasma volume expander by inducing tissue oedema (including the injured brain), albumin may be criticised as being less effective as plasma volume expander in the traumatized patient than previously believed. However, based on arguments given below, albumin is still recommended in the LC if used properly.

Blood volume expanders

There is a risk that activation of the baroreceptor reflex during hypovolemia will cause release of catecholamines into the plasma and adverse vasoconstriction in the penumbra zone with aggravation of the hypoxia. Even though the penumbra zone most likely lack myogenic response and autoregulation it still can response to alpha-stimulation from humoral catecholamines (Edvinsson et al., 1976). The LC therefore recommends

avoidance of hypovolemia by a combination of albumin and saline as plasma volume expanders, and the use of blood transfusions at low haemoglobin (Hb) concentration (see below).

By using albumin (preferably 20%) and always isotonic solutions, the amount of crystalloids can be reduced. Limitation of crystalloids will result in less general tissue oedema, including oedema in the injured brain with a disrupted blood-brain barrier, as a crystalloid solution is distributed to the whole extracellular space. A study on rats suffering a fluid percussion brain trauma also showed that cortical water content was higher if a crystalloid solution was used as plasma volume expander than when an isotonic albumin solution was used (Jungner et al., 2010). A study on meningitis in the cat has shown lower ICP with 20% albumin than with saline as plasma volume expander in volumes resulting in the same plasma volume expansion (Jungner et al., 2011). A clinical study on sTBI patients using albumin as plasma volume expander also showed good outcome (Rodling-Wahlström et al., 2009).

A subgroup analysis from a larger study of patients in the intensive care (the SAFE-TBI study) has, however, shown that large volumes of albumin infusion using hypotonic 4% albumin solution gave adverse effects on outcome compared with when using saline in sTBI patients (SAFE study investigators, 2007). The result of the SAFE-TBI study was most surprising, considering that albumin is the natural plasma protein and that leakage of

this large protein molecule to the injured brain is very small. This is also indicated by the low protein concentration of only 1–2 g/L in cerebrospinal fluid in head-injured patients irrespective of whether albumin is given or not. Compared to a protein concentration of about 60 g/L in plasma, such low values must be insignificant for filtration via altered transcapillary oncotic pressure. The reasons for worse outcome with albumin in the SAFE-TBI study are not clarified. Perhaps the worse outcome observed with albumin in the SAFE-TBI study is more a result of extracranial considerations than intracranial ones. The frequent use of high doses of noradrenaline in that study may also have affected the results in the albumin group negatively by increasing the loss of proteins across the capillary membrane as will be described below.

Several studies have indicated beneficial effects of albumin to head injury (Tomita et al., 1994; Belayev et al., 1999; Bernard et al., 2008), and the post hoc SAFE-TBI study is the only study so far showing adverse effects. Its original database, however, was not designed to meet any specific set of TBI-related criteria and there was an unclear subgroup selection of TBI patients. It has also been criticised for differences in baseline data between the 2 groups, and the fact that the albumin used was hypotonic, which may increase the risk of brain oedema development (Drummond et al., 2011; Van Aken et al., 2012). Possible side effects of albumin, however, may be reduced by using isotonic solutions and with measures reducing the need for plasma volume expander. Potential measures to reduce the need for plasma volume expanders, based on basic physiological principles of transcapillary

fluid exchange in tissues outside the brain, are included in the Lund Concept and will be described below.

Principles of transcapillary exchange in tissues outside the brain

There is always a continuous loss of plasma fluid to the interstitium, called the transcapillary exchange rate (TER). Under normal circumstances, the TER for albumin is 5–6% of the total amount of albumin in plasma per hour, which can increase by 2–3 times during sepsis/SIRS and after a trauma (Fleck et al., 1985). Also, a patient with an isolated head trauma suffers from a general increase in plasma leakage. Normally, the transcapillary leakage of fluid is transferred back to the circulation via the lymphatic system, so that the plasma volume and the interstitial volume are maintained at a normal level. After a trauma and during sepsis/SIRS with increased transcapillary leakage, the recirculation capacity of the lymphatic system may be exceeded and hypovolemia and interstitial oedema will develop. This means that supporting the recirculating effect of the lymphatic system, e.g. by physiotherapy, may be one step to reduce hypovolemia.

The mechanisms of transcapillary fluid exchange can be described with the 2-pore theory (Rippe and Haraldsson, 1994), which is illustrated schematically in Figure 2. According to this theory, the capillary membrane consists of small pores covering the whole capillary network that are only

permeable to small solutes, and much less common large pores that are also permeable to larger molecules such as proteins. The large pores exist only at the end of the capillary network and in venules. In sepsis/SIRS and following trauma, there is an increase in the number of large pores, which explains the increased loss of plasma fluid and proteins to the interstitium and that the plasma volume expanding effect of plasma volume expanders is reduced. The hydrostatic and oncotic Starling forces control fluid through the small pores. The continuous leakage of proteins through a large pore means that the transcapillary oncotic pressure across the large pore is close to zero and the hydrostatic pressure force is the only force for transcapillary fluid exchange through that pore. This means that the hydrostatic capillary pressure is the dominant driving force for filtration in the large pores, and proteins will follow the fluid stream mainly by convection (Rippe and Haraldsson, 1994). According to this theory, an increase in hydrostatic capillary pressure—e.g. due to an increase in arterial pressure or a postcapillary vasoconstriction by infusion of noradrenaline or phenylephrine—will result in an increased loss of plasma fluid through both the small and large pores, and an increased loss of plasma proteins via the large pores aggravating hypovolemia. **The loss of plasma fluid at an increased hydrostatic capillary will be still larger at a state of increased permeability.** This theory has been confirmed both experimentally and clinically (Dubniks et al., 2007; Nygren et al., 2010).

Consequently, a fast infusion rate of a plasma volume expander should result in a greater loss of plasma volume to the interstitium than a slow

infusion rate, as there will be a period of greater increase in arterial pressure at a fast rate. These hypotheses have been confirmed in experimental studies on the septic rat and guinea pig, which showed greater loss of plasma volume when the infusion of albumin was given at a fast rate than when given at a slow rate (Bark et al., 2013; Bark and Grände 2014).

By limiting the volumes of infused albumin, possible adverse effects of albumin can be reduced and albumin may be more effective as plasma volume expander. Suggested measures for reduction of plasma leakage are summarized in Table 1.

Blood transfusion

Patients with a traumatized brain may represent a population of patients particularly susceptible to anemia and hypovolemia. Erythrocytes are essential not only for oxygenation of the brain, but also for the maintenance of normal blood volume, as they contribute to a large proportion of the intravascular volume. Several studies have shown improved oxygenation of the brain after red blood cell transfusion (Ekelund et al.; 2002, Smith et al.; 2005, Dani et al., 2010; Sandal et al., 2013). Transcapillary leakage is also less at a high Hb concentration than at a low one (Valeri et al., 1986, Persson and Grände, 2005). The mechanism may be that there is a larger intravascular volume to be replaced by plasma volume expanders to maintain normovolemia at a low Hb concentration, also resulting in

increased leakage to the interstitium – the more plasma volume expander given, **relatively** more will leak to the interstitium. A post hoc subgroup analysis of the Transfusion Requirements in Critical Care (TRICC) trial analysed effects of blood transfusion in TBI patients (McIntyre et al., 2006). It showed a non-significant improved outcome in the group with liberal transfusion strategy (17 vs 13% in 60 days mortality), and this in spite of the fact that the blood given was not universally leukocyte-reduced. There is strong support from the literature that blood of generally high quality (short storage time) and leukocyte-depleted blood should be used to reduce side effects from the blood transfusions and improve outcome (Bilgin et al., 2011; Gauvin et al., 2010; **Hébert et al., 2003**). **The mechanisms behind the adverse effects of transfused leukocytes are not fully clarified, but they may result in a proinflammatory microvascular effect leading to important clinical consequences (Hébert et al., 2003).**

It should be mentioned, however, that the outcome results from studies of blood transfusion in general are deviating. A study by Hébert et al. showed a tendency of worse outcome in patients with critical illness with a liberal compared to a more restrictive use of blood (Hébert et al., 1999). This study, however, also showed that patients with acute myocardial infarction and unstable angina showed beneficial effects of blood transfusion. This situation may show some similarity with the development of a contusion/penumbra zone area for the injured brain. The use of blood transfusion to severely ill patient was also questioned in a metaanalysis (Marik and Corwim, 2008). In a retrospective study

on a total of 1150 head injured patients it was concluded that the patients given blood had worse outcome (Salim et al., 2008). However, it also showed, that anemia per se was a risk factor. The study can be criticised by the fact that the anemic patients given blood were older, were more severely injured from start and had a lower Glasgow Coma Scale. Restrospective and metanalytic studies on blood transfusion, such as the study by Maric and Corwin (2008) and Salim et al., (2008) can be questioned by the fact that blood transfusion may be a marker of degree of illness. It is notable that none of the referred studies, which indicated worse effects of blood transfusion, used leukocyte-depleted blood. It is reasonable to believe that sTBI patients, in which oxygenation of the injured areas of the brain is most important for outcome, cannot be compared with general intensive care patients regarding effects of blood transfusion.

These results and considerations all taken together give support for the view that transfusion with leukocyte-depleted blood with generally high quality to sTBI patients is beneficial and transfusion to a relatively normal Hb concentration of 15-20 g/L is therefore recommended in the LC.

Treatment to improve perfusion

A microdialysis study involving 48 severely head-injured patients with a raised ICP given treatment according to the LC showed a gradual trend

towards normalisation of lactate/pyruvate ratio and of glycerol concentration in the penumbra zone from raised levels (Ståhl et al., 2001). The results can be interpreted as improved oxygenation and decreased cell destruction, which occurred in spite of a reduced CPP. The most reasonable explanation is that the LC advocates avoidance of hypovolemia by adequate use of plasma volume expanders, by reducing transcapillary leakage, by blood transfusions at low Hb concentrations and by avoidance of noradrenaline-induced vasoconstriction, all **measures** which should result in improved perfusion and oxygenation (see Table 1). If ICP is lowered simultaneously, it will also improve the perfusion. This may illustrate the physiological principle that perfusion of a tissue cannot only be related to the perfusion pressure, but it is also highly dependent on the vascular resistance. While LC primarily counteracts the vasogenic brain oedema by its antihypertensive therapy and the use of albumin, it may also counteract the cytotoxic oedema by improved perfusion and oxygenation.

The use of prostacyclin given intravenously (1-1.5 ng/kg/min) has become an option in the LC to improve perfusion (Grände et al., 1997, Grände, 2006). The option is supported by 2 microdialysis studies showing improved oxygenation of the penumbra zone by prostacyclin (Grände et al., 2000, Reinstrup and Nordström, 2011).

Avoidance of hypovolemia with a combination of albumin, crystalloids and blood transfusion, and avoidance of vasoconstrictors may also improve

perfusion in the rest of the body, such as the intestine, the lungs and the kidneys (Hinshaw, 1996).

Osmotherapy

Osmotherapy is not recommended as a general therapy in the LC, due to lack of scientific and physiological support and side effects. Its use can be followed by a rebound increase in ICP, and is associated with renal failure and severe hyperkalaemia (Grände and Romner, 2012). Osmotherapy may still have a place in release of a menacing brain stem herniation, e.g. in the ambulance or under transportation to the operating room.

Lung function

The LC includes several lung-protective components. High-dose barbiturate therapy is not used as it may trigger pulmonary insufficiency and high fever. Avoidance of the proinflammatory substance noradrenaline (**Miksa et al., 2005**) may reduce the development of pulmonary failure (Contant et al., 2001), like inhibition of the proinflammatory substance angiotensin by angiotensin II antagonist (Ruiz-Ortega et al., 2001). Atelectasis are reduced by inhalation and moderate bagging (under ICP control), and positive endexpiratory pressure (PEEP). PEEP is obligatory in the LC (Grände, 2006). PEEP is safe for the brain, as the venous pressure-increase by PEEP is not transferred to the brain as long as ICP is above the extradural venous pressure (Kongstad and Grände 1999). Limited use of crystalloids reduces

the risk of lung oedema. It has also been reported that ARDS is significantly more common in TBI patients treated with vasopressors in order to elevate CPP (Robertson et al., 1999, Contant et al., 2001). Hyperventilation is not used, as it may aggravate the hypoxia in injured areas of the brain (Muizelaar et al., 1991).

Anti-stress therapy

Head injured patients are severely stressed with a markedly raised concentration of catecholamines in plasma (Clifton et al., 1981). To avoid stress-induced increase in ICP and release of catecholamines, the patients are sedated with midazolam and analgetics in combination with clonidine, and stress-induced wake-up tests are not used (Grände, 2006; Olivecrona et al.; 2009 Skoglund et al., 2012,). A beneficial side effect of this sedation regime is the lack of epileptic seizures, and there is no indication for using prophylactic anti-convulsary treatment (Olivecrona et al., 2009).

Temperature

Therapeutic cooling is neuroprotective, but at the same time it has potential side effects in terms of stress and release of catecholamines, which may compromise cerebral circulation of the penumbra zone. The stress, seen as shivering, is initiated by the difference between body temperature and the temperature value set by the thermostat. Active cooling is also associated with coagulation disturbances and rebound increase in ICP during

rewarming. To date, there is no scientific support for therapeutic hypothermia in TBI patients (Sydenham et al., 2009; Sandestig et al., 2014). Active cooling is therefore not used in a LC-based treatment, and high fever (above 38°C) is instead treated pharmacologically with paracetamol and sometimes **one** bolus dose of Solumedrol followed by more careful control of blood glucose (Grände, 2006; Grände, 2011).

Nutrition

The LC recommends mainly enteral and low energy nutrition **corresponding to slightly more than basal metabolism under sedation** (15 - 20 kcal/kg/24 h for adults, relatively more energy to children) to prevent over nutrition with haemophagocytosis and fever (Roth et al., 1993).

Drainage of cerebrospinal fluid and decompressive surgery

Drainage of cerebrospinal fluid (CSF) is acceptable, but it should be used with caution from a relatively high level, as it may induce transcapillary filtration when the reduced tissue pressure increases transcapillary pressure. Thus, the loss of CSF volume can be replaced by more oedema, with risk of ventricular collapse (Grände, 2006).

Decompressive craniotomy has become relatively common during the last

decade to brake a menacing brain stem herniation. However, it carries the risk of herniation and strangulation in the cranial opening when the counter pressure is lost. By keeping a relatively low CPP combined with normal plasma oncotic pressure, swelling in the cranial opening may be reduced. It was shown in a study from 2007 using the LC that outcome was not worse in patients with decompressive craniotomy than in those without craniotomy, in spite of a higher ICP (Olivecrona et al., 2007). Decompressive craniotomy is a potential life-saving measure to prevent brain stem herniation at a therapy resistant to high ICP (Grände, 2006).

Clinical outcome studies

The Lund concept

Table 1 summarises clinical outcome data from the referred outcome studies published papers on clinical outcome.

The first clinical report (Study I) on the use of a new concept for the treatment of patients with severe TBI and refractory high ICP was published from Lund University Hospital in 1994 (Asgeirsson et al., 1994). This study included patients with refractory ICP and impaired cerebral vasoreactivity to hyperventilation, symptoms previously shown to be compatible with poor prognosis (Schalén et al., 1991).

From Umeå University Hospital one prospective study using the Lund concept is published in two papers, the first on the short term outcome

(Olivecrona et al. 2009) and the second on long time clinical outcome (Olivecrona et al. 2012). Both these papers show low mortality and a favourable outcome (GOS 4 -5) in more than 50% of the treated persons.

Two more prospective non-randomised studies are published, one from the University Hospital in Lund (Eker et al. 1998) and one from the University Hospital in Umeå (Stenberg et al. 2013). The results from the Eker et al. study showed improved outcome results when compared with a historical control group from the same intensive care unit (Schalén et al., 1992). Both papers describe a low mortality and large number of favourable outcomes.

Three retrospective studies, in all including 131 patients with severe traumatic TBI treated have been published (Naredi et al. 1998; Naredi et al. 2001; Olivecrona et al. 2007). All of the three papers present low mortality and a high number of favourable outcome.

One retrospective study on the use of the LC in children with severe TBI has been published from the University Hospitals in Umeå and Gothenburg (Rodling Wahlstrom et al. 2005). This paper presents a mortality of < 10 % and a high number of favourable outcome.

Modified Lund concept

Two randomised studies have compared an ICP-targeted therapy, i.e. a modified version of the LC, with a more traditional CPP-targeted treatment.

The first study was performed from 2006 to 2008 at the University of Sarajevo, Bosnia, and involved 60 brain-injured patients less than 70 years of age (30 per group) after severe TBI or aneurysmal subarachnoid haemorrhage (SAH) (Dizdarevic et al., 2012). The authors included nimodipin for blood pressure control in the modified LC arm and they also allowed the use of hypertonic saline. In the CPP-targeted arm, the CPP goal was a CPP above 70–80 mmHg and vasopressors and mannitol were frequently used. In both arms, seizure prophylaxis with fenytoin was given. Patients treated with the ICP-targeted therapy had a mortality rate of 20%, as opposed to 43% for the patients treated with a more conventional CPP-targeted therapy based on Brain Trauma Foundation guidelines from 2000 ($p = 0.03$). The proportion of children with favourable outcome (GOS 4–5) in the ICP-targeted group was 53%, and it was 40% in the CPP-targeted group.

The second randomised study was performed in Hangzhou First People's Hospital, Hangzhou, China. It included 68 traumatically brain-injured patients with a GCS of < 9 who were divided into 2 groups that did not have significantly different baseline data regarding age, initial GCS, and Acute Physiology and Chronic Health Evaluation (APACHE II) score. In one

group, the treatment followed the main principles of the LC (n = 30, treated between 2006 and 2009), and conventional treatment was used in the other group (n = 38, treated between 2004 and 2006). A 28-day mortality rate of 30% was found in the LC group and it was 57% in the conventionally treated group ($p < 0.05$) (Liu et al., 2010).

The Lund concept and meningitis

Finally, the LC has been used in patients with severe meningitis in 2 studies. Twelve patients with a GCS of < 9 and an ICP above 20 mmHg were included in one of the studies. Two of the patients died, resulting in a mortality rate of 20% (Grände et al., 2002). The remaining 10 patients recovered to a GOS of 4-5. Fifteen patients with a GCS score of < 9 were included in the other study, and all but one had elevated ICP. Ten patients survived, resulting in a mortality rate of 33% (Lindvall et al., 2004). These results can be compared with a previously reported mortality rate of 62% in a comparable group of meningitis patients (Schutte and van der Meyden, 1998).

Discussion

The presented outcome studies **in this review** reflect outcome results of patients treated from **1989** up to 2013; they show favourable outcome in 64–80% of patients, which are good results compared to those from outcome studies with other treatments during the same time period. Two large

randomised head-injury trials (Clifton et al., 2001), from the 1990s and later, showed mortality rates of around 28% and unfavourable outcomes of 57%.

Among the best results reported during the time span of the above-mentioned LC studies were those from the study by Rosner and co-workers, involving 157 patients (Rosner et al., 1995), which showed a mortality rate of 29% and a proportion of patients with favourable outcome (GOS 4–5) of 59%.

The data from one of the studies above (Study VI, **Table 1**) (Olivecrona et al., 2009) involving 48 patients were entered into the prognostic calculators of the IMPACT study group (Steyerberg et al., 2008) and the CRASH study group (MRC CRASH, 2008). Both analyses showed that the patients had a more favourable outcome than could have been anticipated from the prognosis instruments (Olivecrona and Koskinen, 2012; Olivecrona and Olivecrona, 2013). The new validation of the IMPACT prognostic calculator was recently published, using data from several newer head-injury trials (Roozenbeck et al., 2012). This validation showed that the prognostic model of the IMPACT group is still valid, and one may therefore draw the conclusion that the results for patients treated according to the LC were not worse than for patients treated according to any other guidelines.

In studies III, IV, V, VI, VII and VIII (**Table 1**), patients with a GCS of 3 were included. In the same studies, the only exclusion criterion regarding

neurological status of the patients included, was a first-measured CPP of 10 mmHg or less, i.e. patients with unilaterally or bilaterally dilated and fixed pupils were allowed into the study. In many head-injury trials, patients are excluded if they have dilated or fixed pupils, deemed to not survive the next 24 hours—or even a GCS of 3.

A recent study involving patients from the state of New York has shown that outcome for severe head trauma has been improved from a 2-week mortality of 22% in 2001 down to 13.3% in 2009 using treatments according to US Brain Trauma Foundation guidelines (Gerber LM et al., 2013). The outcome results at the end of the period appear to approach those with the LC from 1988 to 2011, as presented in this review.

The aim of this review was to present the principles of the Lund Concept as it is today together with all clinical outcome studies published with the Lund concept so far. This means that we have presented also components, which still lack definite scientific support from clinical studies (e.g the use of blood transfusion and albumin therapy). The LC was initiated around 1990 as a therapy mainly based on basal physiological principles, i.e. for brain volume and brain perfusion regulation, and the guidelines were published 4 years later (Asgeirsson et al. 1994). The conventional therapy used at that time in many aspects was not in agreement with basal physiological principles and mortality was very high and around 40-50%. Since then, the

principles of the LC guidelines have not changed, except that dihydroergotamin is not included any more. At its introduction the LC had no other scientific support than its physiological base, but thereafter, as discussed in this review, several experimental and clinical studies have been performed giving support for the principles of the concept. The main disadvantage with the LC is that it has still not been compared with other guidelines in well-performed large randomized clinical outcome studies. However, in spite of several efforts to perform a larger clinical randomised study both in Europe and US, it appeared impossible for logistic, practical and ethical reasons. In the middle of the 90th and later, other guidelines were introduced such as the Brain Trauma foundation guidelines followed by revisions (Bullock et al., 1996; Bullock et al., 2000; Brain Trauma Foundation, 2007), European guidelines (Maas et al., 1997), the Addenbrooke's guidelines (Menon, 1999) and the Japanese guidelines (2012). They are more based on a metaanalytic approach but, like the Lund Concept, these guidelines have not been tested in a randomised clinical trial. This means that neither the Lund Concept nor other guidelines regarding outcome can be compared from a strict scientific support except than from smaller outcome studies. All clinical outcome studies with the Lund concept so far are small and each of them alone therefore is of moderate or small scientific value. However, if taken all outcome studies together they strongly indicate that the Lund concept is a successful therapy. We believe that LC may optimise the possibility for the brain to recover

after sTBI and thus better utilise the compensating mechanisms resulting in acceptable clinical outcome.

Summary

Several clinical studies have shown that the Lund concept, which is mainly based on physiological principles, such as principles for brain volume and brain perfusion regulation, works well in the treatment of severe head injury and gives results that are not worse than the best results reported for any other treatment guideline.

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Legends

Figure 1. A simplified schematic algorithm of the LC used in the clinical setting. For doses of the pharmacological substances used and other parameters, see Grände, 2006.

Figure 2. Schematic illustration of a capillary outside the brain, describing the 2-pore theory of transcapillary fluid exchange. It shows the frequent small pores that are permeable to water and small solutes, and the fewer large pores at the end of the capillary network, which are also permeable to proteins. Erythrocytes are not shown. Note that there is no oncotic absorbing force across the large pores ($\Delta\pi \approx 0$), which means that the hydrostatic transcapillary pressure (ΔP) will create a force for convective protein-rich volume flow through each large pore. The increase in the number of large pores after trauma will increase the loss of proteins.

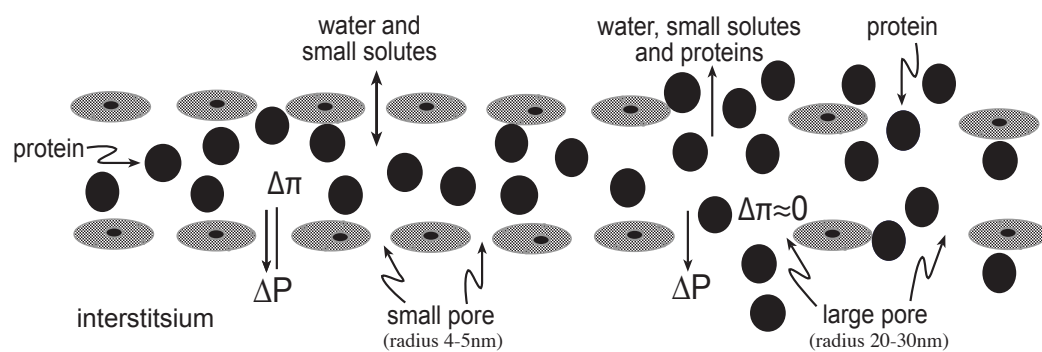


Table 1. Potential measures to reduce transcapillary leakage of albumin in the body outside the brain

Avoid high arterial pressures and CPP
Avoid the use of vasopressors
Use low infusion rates of albumin
Use higher concentrations of albumin (20%)
Avoid low haemoglobin concentrations
Increase the capacity of the lymphatic system by physiotherapy

Table 2

Study Nr	Author	Year	Study type	Inclusion criteria	Number of Patients	Follow up time (months)	Mortality (GOS 1) (%)	Favourable outcome (GOS 4 – 5) (%)
I	Asgeirsson et al.	1994	Observational	GCS < 8 Impaired CO ₂ reactivity ICP > 20	11	8	18.1	81.8
II	Eker et al.	1998	Prospective, Non-R	GCS < 8 ICP > 25	53	6	7.5	79.2
III	Naredi et al.	1998	Retrospective	≤ 70 yrs GCS ≤ 8 CPP > 0	38	12	13.1	71.1
IV	Naredi et al.	2001	Retrospective, Consecutive	15-70 yrs GCS ≤ 8 CPP > 5	31	> 10	3.2	70.0
V	Olivecrona et al.	2007	Retrospective	< 75 yrs GCS ≤ 8 CPP > 10	93*	N/A	14.1	63.0
VI	Olivecrona et al.	2009	Randomised, Prospective	15-70 yrs GCS ≤ 8 CPP > 10	48	3	12.5	52
VII	Olivecrona et al.	2012	Randomised, Prospective	15-70 yrs GCS ≤ 8 CPP > 10	48#	24		62
VIII	Stenberg et al.	2013	Prospective, Observational	17-64 GCS ≤ 8			14	N/A†
IX	Rodling Wahlstrom et al.	2005	Retrospective	< 15 yrs GCS ≤ 8	41	N/A [⊥]	7.5	80.0

Non-R = Non-Randomised, N/A = Not Available, * =31 of the patients were also included in Study nr IV., # = same patients as in study VI, † = GOS 5 (Good outcome) 31 %, ⊥ = median 12 months in survivors